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## ORIGINAL ARTICLES.

### METABOLIC STUDIES IN ADDISON'S DISEASE: THE EFFECT OF TREATMENT WITH THE CORTICAL HORMONE OF THE SUPRARENAL GLAND.

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The first positive information regarding the function of the suprarenal glands was obtained with the description of the clinical syndrome now known as Addison's disease. Of recent years there have been many attempts to reproduce this syndrome in animals by extirpation of both suprarenal glands, but the animal (dog or cat) invariably died, usually within 2 weeks. In this respect the experimental picture more nearly corresponds to that seen in cases of suprarenal apoplexy rather than that seen in Addison's disease, which usually runs a subacute or chronic course. In consequence, it was commonly considered that the clinical syndrome of Addison's disease could not be reproduced experimentally in animals. Recent investigators,[4,37] however, have maintained that many of the phenomena of Addison's disease are similar to those observed in supra-

renalectomized animals. Whereas many symptoms vary in severity in the two conditions, they are qualitatively the same and are to be considered as manifestations of suprarenal insufficiency. Weakness, muscular asthenia, loss of weight, anorexia, gastrointestinal disturbances, and nervous manifestations in particular, are often found both in clinical and experimental conditions.

Extended chemical and metabolic studies have been made of suprarenalectomized animals, and the changes observed have been interpreted in terms of the normal physiologic activity of the suprarenal gland. These studies recently have been reviewed by Britton, and will not be considered in detail here. The clinical features of Addison's disease have been reported in detail by Rowntree and Snell. Thus far, 125 patients with Addison's disease have been observed at The Mayo Clinic. The suprarenal cortical hormone prepared by the method of Swingle and Pfiffner has, in the last year, been used in the treatment of 20 patients. We shall report here both on the chemical and metabolic changes observed in cases of Addison's disease, and on the effect on these changes of treatment with the suprarenal cortical hormone.

When both suprarenal glands are removed from an animal, whether by means of an operation in one stage or in two stages, suprarenal insufficiency becomes complete with the stroke of the surgeon's knife. The subsequent clinical course is rapidly downward to a fatal termination. The course of the patient with Addison's disease shows many points of similarity, yet the differences are characteristic and fundamental. For the purposes of this consideration the course may arbitrarily be divided into three periods. The distinction between these periods is not always sharp, but they usually are recognizable.

**The Three Periods in the Course of Addison's Disease.** *The Period of Initial Destruction of the Suprarenal Glands.* Approximately two-thirds of all cases of Addison's disease are due to tuberculosis of the suprarenal glands. One-fifth of the total number are due to atrophy, particularly of the cortex. Experimental studies have disclosed that removal of one suprarenal gland may be compatible with the life of the animal and that bilateral suprarenalectomy is not necessarily fatal if accessory glandular tissue is present. The suprarenal glands in many cases of Addison's disease in which there is a history indicating duration limited to a few weeks, are represented by large caseous or calcareous masses suggestive of a chronic, slowly growing lesion. These observations all suggest that the suprarenal glands possess considerable functional reserve, and that clinically recognizable signs of Addison's disease do not appear until this reserve is seriously impaired or destroyed. When the functional activity of the glands becomes insufficient for the daily physiologic requirements of the body, the second stage is initiated.

*The Period of the Recognizable Clinical Syndrome.* The characteristic clinical symptoms of Addison's disease, namely, asthenia, pigmentation, loss of weight and strength, and arterial hypotension, are well known. Once they appear the diagnosis is established. Although the efficiency and activity of the patient may be greatly reduced, disability is not necessarily complete. The average length of life following the appearance of the clinical symptoms of Addison's disease is 16.5 months, according to Rowntree, and 13.3 months according to Guttman, although Guttman reported 11 cases in which the duration was more than 5 years. A greater or lesser degree of suprarenal insufficiency must be present during this period, yet the patient is in a fairly satisfactory clinical condition. When we mention the chemical and metabolic changes in Addison's disease, it is to this period that we refer.

*The Terminal Period or Crisis.* Patients with Addison's disease are exceedingly susceptible to intercurrent infection, and usually are sensitive to fatigue and minor traumas, such as dental extraction. Such predisposing factors frequently initiate an acute, shock-like condition, or a period of crisis, although the latter may also develop spontaneously. This condition is characterized by a severe gastrointestinal upset, nausea and vomiting, pain, circulatory collapse, low blood pressure, cold extremities, and lowered bodily temperature. The urinary output is often reduced and the respiration may have the characteristic irregularity described by Rowntree.

The outcome of such a crisis varies with the severity of the condition. In some cases several such upsets have occurred from which the patients have recovered spontaneously. In other cases, treatment as outlined in the reports of Rowntree, Greene, Swingle and Pfiffner and of Rowntree, Greene, Ball, Swingle and Pfiffner, is strikingly beneficial. Still other patients are refractory to treatment, and the crisis is terminal.

The chemical and metabolic determinations in Addison's disease will be presented on the basis of the last two periods. The change from the one to the other may be insidious, and there is room for difference of opinion so far as the precise severity of symptoms necessary for the establishment of a crisis is concerned, but in general the distinction between the two groups is permissible.

**The Basal Metabolic Rate.** The respiratory exchange of patients with Addison's disease was first studied by Fuchs and Roth. Löffler, Muirhead, Aub, Forman and Bright, Grafe, Lawrence and Rowe, and Labbé and Stévenine reported cases in which the basal metabolic rate was reduced. Herman and Richard, and Marañon and Carrasco reported other cases in which the metabolic rate was normal or increased. A considerable number of cases was reported by Boothby and Sandiford and by Rowntree. These reports indicate that the basal metabolic rate in this condition, although frequently within

normal limits, is variable, and may be markedly reduced in some cases. We wish to summarize the experience at The Mayo Clinic to date, with the report on the basal metabolic rate in a series of 86 cases of Addison's disease. A preliminary study indicated that the basal metabolic rate, when calculated according to the Aub-Du Bois standard in the usual way, fell, for the most part, within the lower limits of normal. Experience at the Clinic, however, has indicated that the mean basal metabolic rate of normal persons varies, depending on the age group studied. In younger persons it may be from −3 to −7 per cent. Under these conditions it becomes

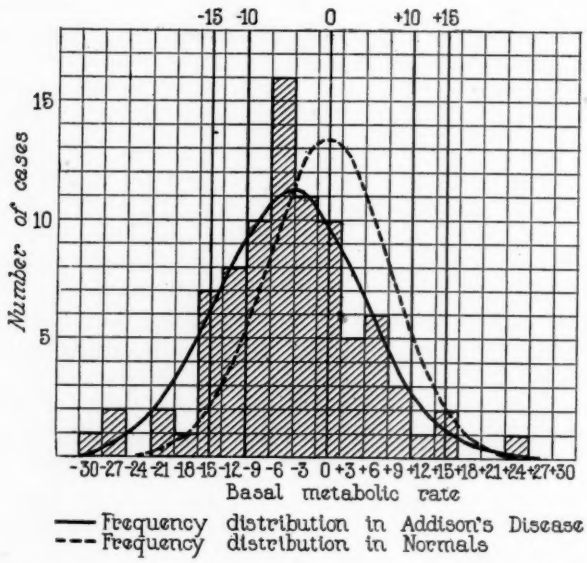


FIG. 1.—The frequency of distribution of basal metabolic rates in a series of 86 patients with Addison's disease. The calculated distribution curve is shown: mean, −4.8 ± 0.67; standard deviation, 9.2 ± 0.48. The distribution curve for normal men aged 40 to 44 years is given for comparison: mean, 0.0 ± 0.34; standard deviation, 7.7 ± 0.24.

difficult to judge of the statistical validity of the apparent reduction of the basal metabolic rate observed in cases of Addison's disease. To facilitate comparison the latter rates were recalculated according to the new standards of Boothby and Sandiford. The frequency distribution is shown in Fig. 1, together with the distribution curve found by Boothby and Sandiford for normal men aged 40 to 44 years.

The basal metabolic rate unquestionably is reduced in Addison's disease, with a mean value of approximately −5 per cent and a mode of approximately −7 per cent. Very low values are found in certain cases, and there is a suggestion that these low values are more

frequently found in crisis. The condition of the patient in crisis, however, precludes any very extended study of respiratory exchange at that time.

It is generally recognized that the basal metabolic rate is reduced to the extent named, or more, in conditions characterized by undernutrition. Loss of weight and muscular asthenia are cardinal symptoms in Addison's disease, and the reduction in respiratory exchange in consequence may be a secondary phenomenon, although we have not found direct correlation between the loss in weight and the basal metabolic rate.

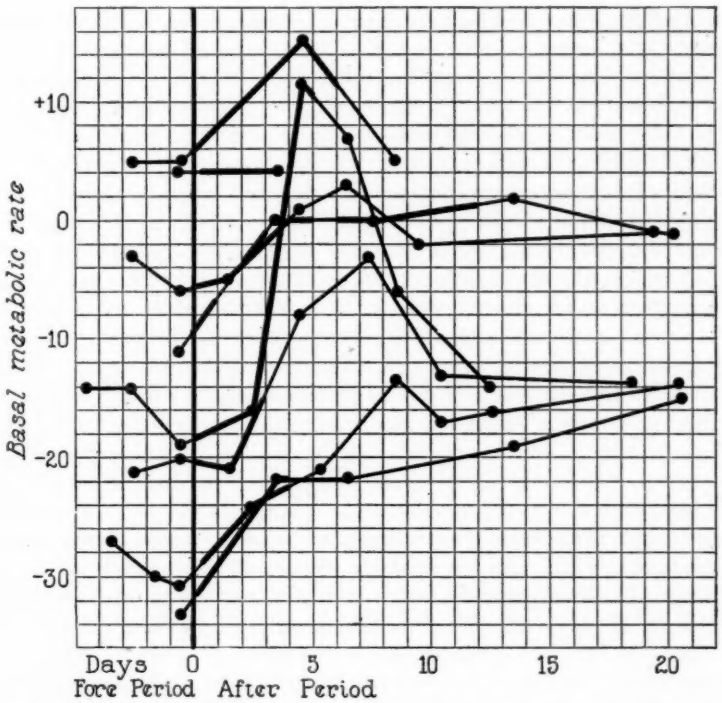


FIG. 2.—Changes in the basal metabolic rate of patients with Addison's disease treated with the suprarenal cortical hormone. The days on which treatment was given are marked by the heavy line.

Investigators who have determined the respiratory exchange in animals after suprarenalectomy have considered the changes to be direct results of the suprarenal insufficiency. The earlier studies were discordant, but Aub, Forman and Bright, Houssay and Artundo, Swingle, Pfiffner and Webster, and Harrop, Pfiffner, Weinstein and Swingle all have reported reduction in the basal metabolic rate. The last-named investigators found that the basal

metabolic rate of animals which had reached the stage of prostration was approximately 50 per cent below normal. Forty-eight to 72 hours after administration of the cortical hormone the metabolic rate rose to between 10 and 18 per cent above the normal previously established for an individual animal.

The effect of treatment with the cortical hormone on the metabolism of patients with Addison's disease (Fig. 2) is variable. There is very little change in patients whose metabolic rate is normal. When the metabolic rate of the patient is reduced, treatment causes elevation toward, although not always to within, normal limits: thus in Case 12 the change was from −31 to −13 per cent and in Case 16 from −22 to −4 per cent. The maximal increase was from −18 to +12 per cent, and in no case did the basal metabolic rate after treatment rise above +14 per cent. The increase in the basal metabolic rates of these patients may in part be associated with the increased strength and vitality of the patient, but this is not necessarily the case, for we have observed marked clinical improvement associated with considerable gain in weight without any corresponding change in the metabolic rate.

That the change in the respiratory exchange is not an accurate guide to the clinical condition is also indicated by 3 cases in which there were considerable increases in metabolic rate, with only a questionable degree of clinical improvement.

The study of the respiratory exchange of this group of patients shows that the clinical features are in harmony with experimental results in indicating some degree of reduction in the basal metabolic rate in the presence of suprarenal insufficiency, and in demonstrating improvement following treatment with cortical extract. The results with patients, however, are much less marked than are those with animals, and do not serve to determine whether these changes are direct results of the suprarenal insufficiency or whether they are secondary to the associated nutritional disturbance.

**Nitrogen Metabolism.** The earliest studies of the composition of the urine and of the nitrogen balance in Addison's disease, as pointed out by Grafe, may be discounted because of the inadequacy of the analytic methods then available, even though the results were not significantly different from normal. The more recent investigations, such as those of Kolisch and Pichler, Senator, Vollbracht, Pickardt, Wolf and Thacker, Eiselt, and Beuttenmüller and Stoltzenberg, are free from this objection.

We have studied the partition of urinary nitrogen and the approximate nitrogen balance in 9 cases of Addison's disease, before, during, and after treatment with the suprarenal cortical hormone. Because of the anorexia and gastrointestinal distress that accompanies many cases of untreated Addison's disease, it has not been possible to put these patients on a constant, rigid diet. It has been necessary, instead, to allow the patient to eat as desired, but all food served

and any uneaten portion was weighed. In this way a record was kept of all food actually consumed. The content of nitrogen and calories was then calculated from the Atwater-Bryant tables. The stools were not saved, but in calculating the nitrogen balance, the fecal nitrogen was assumed to be one-tenth of the intake. Care was taken in the collection of urine, and the periods over which the daily specimens of urine were collected were, for the most part, accurate to within 15 minutes. The analytic methods of Folin were used throughout in urinalysis.

The analytic results in illustrative cases are given in Tables 1, 2, 3, 4, 5 and 6. The details of the clinical histories have been given in the paper of Rowntree, Greene, Ball, Swingle and Pfiffner. For the most part, the composition of the urine corresponded to the lower level of the usually accepted normal standards. The total nitrogen varied between 5.30 and 11.77 gm. for 24 hours. Urea was the major constituent. The values for the creatinin nitrogen, uric acid nitrogen, amino-acid nitrogen and rest nitrogen all fell within the limits of normal, and to this extent served to exclude disturbances in endogenous metabolism. There was no change in these values with treatment. The acid-base balance, as indicated by the hydrogen-ion concentration, the titratable acidity, the ammonia nitrogen or the excretion of phosphate was likewise normal, and was not significantly changed during treatment.

We have found a considerable degree of creatinuria (more than 30 mg. of creatin nitrogen daily, or more than 10 per cent of the preformed creatinin) in 7 of 13 cases studied. When creatin has been present it has been reduced in amount or has disappeared completely as a result of treatment with the cortical hormone (Table 1). Especial mention should be made of the excretion of urea in the ninth case in our experience (Table 3) which, as has been said, is reported in another paper. This patient was weak, but was in a satisfactory clinical condition on the first day of the metabolic study. The second day he had no appetite, ate very little, vomited once, and took only a small amount of fluid; the amount of urine was greatly reduced. Treatment with cortical hormone was started, the intake of fluid was pushed during the next two days, and the patient made a prompt and spectacular clinical recovery. The elimination of practically all urinary constituents was reduced the day the urinary output was diminished. That this was due to retention is shown by the increased excretion the 2 following days. This is well shown by the figures for urea, creatinin and titratable acidity. The output of total nitrogen the second day of the experiment was 5.83 gm. less than on the first day. Approximately this amount of extra nitrogen was eliminated in the next 2 days. The intake of food was reduced during this period. This effect, plus the washing out of retained nitrogen, resulted temporarily in a very markedly negative nitrogen balance.

TABLE 1.—THE EFFECT ON METABOLISM OF TREATMENT WITH CORTICAL HORMONE IN THE SEVENTH CASE OF OUR EXPERIENCE.

| | January. | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 |
| Weight, kg. | 52.4 | 52.4 | 52.8 | 52.4 | 52.4 | 52.6 | 52.6 | 52.8 | 53.8 | 53.4 | 54.0 | 53.8 | 53.8 |
| Cortical hormone, cc. | ... | ... | ... | ... | 14 | 21 | 21 | 20 | 20 | 10 | | | |
| Intake of food: | | | | | | | | | | | | | |
| Total calories | 1120 | 1539 | 1809 | 1936 | 1664 | 1691 | 1862 | 2032 | 2000 | 2000 | 2000 | 2000 | 2000 |
| Protein expressed as nitrogen, gm. | 6.88 | 6.88 | 6.08 | 8.32 | 6.56 | 6.56 | 8.64 | 10.10 | 9.60 | 9.60 | 9.60 | 9.60 | 9.60 |
| Basal metabolic rate, per cent | ... | +5 | ... | ... | ... | ... | ... | ... | +15 | ... | ... | ... | +4 |
| Urine for 24 hours: | | | | | | | | | | | | | |
| Volume, cc. | 750 | 1350 | 850 | 1550 | 650 | 750 | 1350 | 1150 | 950 | 1350 | 1970 | 1000 | 1300 |
| Total nitrogen, gm. | 6.35 | 7.99 | 5.42 | 7.40 | 3.98 | 6.65 | 5.70 | 4.78 | 5.26 | 5.78 | 5.41 | 3.85 | 5.55 |
| Urea nitrogen, gm. | 4.65 | 5.57 | 3.99 | 5.34 | 2.55 | 4.85 | 4.77 | 3.78 | 4.20 | 4.77 | 4.13 | 2.92 | 4.16 |
| Ammonia nitrogen, gm. | 0.25 | 0.46 | 0.19 | 0.27 | ... | 0.28 | 0.21 | 0.18 | 0.23 | 0.19 | 0.25 | 0.12 | 0.24 |
| Total creatinin nitrogen, gm. | 0.37 | 0.66 | 0.31 | 0.46 | 0.25 | 0.47 | 0.40 | 0.31 | 0.30 | 0.35 | 0.32 | 0.26 | 0.35 |
| Preformed creatinin nitrogen, gm. | 0.27 | 0.48 | 0.24 | 0.37 | 0.22 | 0.39 | 0.36 | 0.27 | 0.28 | 0.34 | 0.31 | 0.25 | 0.34 |
| Creatin nitrogen, gm. | 0.10 | 0.18 | 0.07 | 0.09 | 0.03 | 0.08 | 0.04 | 0.04 | 0.02 | 0.01 | 0.01 | 0.01 | 0.01 |
| Amino nitrogen, gm. | 0.16 | 0.29 | 0.17 | 0.26 | 0.19 | 0.23 | 0.06 | 0.05 | 0.08 | 0.08 | 0.06 | 0.07 | 0.10 |
| Uric acid nitrogen, gm. | 0.05 | 0.04 | 0.04 | 0.07 | 0.03 | 0.04 | ... | 0.06 | 0.07 | 0.07 | ... | 0.07 | 0.10 |
| Rest nitrogen, gm. | 0.87 | 0.97 | 0.71 | 0.99 | 0.45 | 0.78 | 0.25 | 0.40 | 0.38 | 0.32 | 0.47 | 0.41 | 0.60 |
| Nitrogen balance, gm. | −0.16 | −1.80 | +0.05 | +0.09 | +1.92 | −0.75 | +2.08 | +4.31 | +3.38 | +2.86 | +3.23 | +4.79 | +3.09 |
| Hydrogen-ion concentration | 5.20 | 5.00 | 5.20 | 4.80 | 6.90 | 5.90 | 5.50 | 5.90 | 5.50 | 5.70 | 6.30 | 6.20 | 5.90 |
| Total acids, cc. N/10 | 212 | 241 | 162 | 208 | 50 | 214 | 168 | 166 | 157 | 198 | 145 | 115 | 170 |
| Phosphate, gm. | 0.40 | 0.51 | 0.34 | 0.39 | 0.25 | 0.44 | 0.34 | 0.31 | 0.37 | 0.36 | 0.30 | 0.28 | 0.34 |
| Sodium chlorid, gm. | 2.73 | 4.12 | 2.72 | 5.22 | 2.81 | 3.71 | 3.72 | 3.33 | 3.99 | 4.19 | 6.60 | 4.52 | 5.89 |
| Blood: | | | | | | | | | | | | | |
| Urea, mg. in each 100 cc. | 40 | ... | ... | 22 | ... | ... | ... | ... | ... | ... | ... | ... | 32 |
| Sulphates, mg. in each 100 cc. | 6.7 | ... | ... | 5.1 | ... | ... | ... | ... | ... | ... | ... | ... | 4.9 |

TABLE 2.—THE EFFECT ON METABOLISM OF TREATMENT WITH CORTICAL HORMONE IN THE EIGHTH CASE OF OUR EXPERIENCE.

| | December. | | | | | January. | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 27 | 28 | 29 | 30 | 31 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 |
| Weight, kg. | 62.10 | ... | 61.80 | ... | 61.70 | ... | 62.10 | 62.10 | ... | 63.90 | ... | 63.00 | ... | 63.00 | ... | 62.80 |
| Cortical hormone, cc. | ... | ... | ... | ... | ... | 10 | 10 | 10 | 15 | 15 | | | | | | |
| Intake of food: | | | | | | | | | | | | | | | | |
| Total calories | 1750 | 2100 | 2700 | 2650 | 2850 | 2500 | 2750 | 2950 | 2300 | 2675 | 2400 | 2700 | 2600 | 2750 | 2400 | 2300 |
| Protein expressed as nitrogen, gm. | 8.00 | 8.80 | 10.40 | 10.40 | 11.20 | 10.40 | 11.20 | 11.20 | 9.60 | 8.80 | 9.60 | 10.40 | 9.60 | 9.60 | 10.40 | 11.20 |
| Basal metabolic rate, per cent | −14 | ... | −14 | ... | −19 | ... | ... | −16 | ... | +12 | ... | +7 | ... | −6 | ... | −12 |
| Urine for 24 hours: | | | | | | | | | | | | | | | | |
| Volume, cc. | 1600 | ... | 1750 | 1610 | 1300 | 1400 | 1410 | 1850 | 1150 | 1150 | Specimen lost. | 1400 | 1230 | 1210 | 1420 | 1510 |
| Total nitrogen, gm. | 11.77 | ... | 10.75 | 9.98 | 8.12 | 8.93 | 8.87 | 9.60 | 7.51 | 7.93 | | 9.90 | 7.93 | 7.72 | 9.16 | 9.96 |
| Urea nitrogen, gm. | 9.73 | ... | 9.04 | 8.37 | 6.85 | 7.36 | 7.42 | 8.35 | 6.16 | 6.47 | | 7.73 | 6.61 | 6.57 | 7.84 | 8.63 |
| Ammonia nitrogen, gm. | 0.37 | ... | 0.15 | 0.14 | 0.09 | 0.37 | 0.14 | 0.22 | 0.20 | 0.42 | | 0.37 | 0.19 | 0.19 | 0.25 | 0.29 |
| Total creatinin nitrogen, gm. | 0.69 | ... | 0.59 | 0.53 | 0.46 | 0.59 | 0.56 | 0.58 | 0.49 | 0.50 | | 0.59 | 0.46 | 0.44 | 0.52 | 0.56 |
| Pref. creatinin nitrogen, gm. | 0.66 | ... | 0.59 | 0.48 | 0.44 | 0.57 | 0.52 | 0.56 | 0.47 | 0.49 | | 0.57 | 0.44 | 0.43 | 0.48 | 0.53 |
| Creatin nitrogen, gm. | 0.03 | ... | ... | 0.05 | 0.02 | 0.02 | 0.04 | 0.02 | 0.02 | 0.01 | | 0.02 | 0.02 | 0.01 | 0.04 | 0.03 |
| Amino nitrogen, gm. | 0.09 | ... | 0.06 | 0.06 | 0.09 | 0.06 | 0.07 | 0.07 | 0.05 | 0.06 | | 0.07 | 0.06 | 0.05 | 0.05 | 0.06 |
| Uric acid nitrogen gm. | 0.16 | ... | 0.15 | 0.14 | 0.12 | 0.12 | 0.15 | 0.17 | 0.15 | 0.15 | | 0.19 | 0.16 | 0.14 | 0.16 | 0.17 |
| Rest nitrogen, gm. | 0.83 | ... | 0.76 | 0.74 | 0.51 | 0.43 | 0.52 | 0.21 | 0.46 | 0.33 | | 0.95 | 0.45 | 0.33 | 0.34 | 0.25 |
| Nitrogen balance, gm. | −4.57 | ... | −1.39 | −0.62 | +1.96 | +0.43 | +1.21 | +0.48 | +1.13 | −0.01 | | −0.54 | +0.71 | +0.92 | +0.20 | +0.12 |
| Total acids, cc. N/10 | 317 | ... | 223 | 239 | 110 | 365 | 340 | 508 | 178 | 121 | | 305 | 142 | 243 | 305 | 247 |
| Phosphate, gm. | 0.97 | ... | 0.93 | 0.75 | 0.49 | 0.60 | 0.86 | 0.87 | 0.65 | 0.74 | | 0.81 | 0.66 | 0.89 | 1.12 | 0.82 |
| Sodium chlorid, gm. | 13.12 | ... | 15.03 | 11.52 | 9.38 | 12.48 | 10.80 | 14.43 | 10.51 | 9.50 | | 14.28 | 10.41 | 9.94 | 8.29 | 14.50 |
| Blood: | | | | | | | | | | | | | | | | |
| Urea, mg. in each 100 cc. | 28 | ... | ... | ... | ... | ... | ... | ... | ... | 30 | | ... | ... | ... | 32 | |
| Sulphates, mg. in each 100 cc. | ... | ... | ... | ... | ... | ... | ... | ... | ... | 6.4 | | ... | ... | ... | 3.5 | |

TABLE 3.—THE EFFECT ON METABOLISM OF TREATMENT WITH CORTICAL HORMONE IN THE NINTH CASE OF OUR EXPERIENCE.

| | January. | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 |
| Weight, kg. | ... | 54.00 | ... | ... | 54.40 | ... | 54.70 | 55.10 | ... | ... | 56.00 | 55.50 | 55.50 |
| Cortical hormone, cc. | ... | ... | 15 | 15 | 15 | 15 | | | | | | | |
| Intake of food: | | | | | | | | | | | | | |
| Total calories | 2500 | 900 | 700 | 1500 | 1250 | 1950 | 2650 | 2400 | 2650 | 2850 | 2450 | 2600 | 2700 |
| Protein expressed as nitrogen, gm. | 10.40 | 1.60 | 5.60 | 9.60 | 7.20 | 10.40 | 11.20 | 11.20 | 11.20 | 11.20 | 10.40 | 12.00 | 9.60 |
| Basal metabolic rate, per cent | ... | +1 | ... | ... | −7 | ... | +1 | ... | −5 | ... | ... | −9 | |
| Urine for 24 hours: | | | | | | | | | | | | | |
| Volume, cc. | 1400 | 780 | 1500 | 1520 | 1050 | 950 | 1250 | 1100 | 1440 | 1450 | 1300 | 1410 | 1230 |
| Total nitrogen, gm. | 10.56 | 4.73 | 12.24 | 13.52 | 10.25 | 9.65 | 9.98 | 8.44 | 9.51 | 9.16 | 7.73 | 7.54 | 7.65 |
| Urea nitrogen, gm. | 8.85 | 3.67 | 10.36 | 11.53 | 8.63 | 7.65 | 8.25 | 7.41 | 8.43 | 7.79 | 6.65 | 6.33 | 6.69 |
| Ammonia nitrogen, gm. | 0.21 | 0.19 | 0.34 | 0.39 | 0.31 | 0.47 | 0.33 | 0.23 | 0.17 | 0.17 | 0.20 | 0.13 | 0.14 |
| Total creatinin nitrogen, gm. | 0.59 | 0.41 | 0.65 | 0.56 | 0.39 | 0.57 | 0.47 | 0.36 | 0.44 | 0.45 | 0.38 | 0.44 | 0.41 |
| Preformed creatinin nitrogen, gm. | 0.57 | 0.39 | 0.63 | 0.52 | 0.37 | 0.54 | 0.44 | 0.35 | 0.44 | 0.43 | 0.38 | 0.42 | 0.39 |
| Creatin nitrogen, gm. | 0.02 | 0.02 | 0.02 | 0.04 | 0.02 | 0.03 | 0.03 | 0.01 | ... | 0.02 | ... | 0.02 | 0.02 |
| Amino nitrogen, gm. | 0.05 | 0.04 | 0.07 | 0.05 | 0.04 | 0.06 | 0.05 | 0.05 | 0.05 | 0.05 | 0.04 | 0.05 | 0.05 |
| Uric acid nitrogen, gm. | 0.11 | 0.06 | 0.19 | 0.21 | 0.16 | ... | 0.13 | 0.12 | 0.16 | 0.15 | 0.13 | 0.11 | 0.11 |
| Rest nitrogen, gm. | 0.75 | 0.36 | 0.63 | 0.78 | 0.72 | 0.83 | 0.75 | 0.27 | 0.26 | 0.55 | 0.33 | 0.48 | 0.26 |
| Nitrogen balance, gm. | −1.20 | −3.29 | −7.20 | −5.88 | −3.75 | −0.29 | +0.10 | +1.64 | +0.57 | +0.92 | +1.63 | +3.26 | +0.99 |
| Total acids, cc. N/10. | 217 | 83 | 361 | 374 | 230 | 294 | 227 | 178 | 157 | 240 | 236 | 324 | 270 |
| Phosphate, gm. | 0.58 | 0.29 | 0.74 | 0.86 | 0.49 | 0.54 | 0.50 | 0.39 | 0.50 | 0.61 | 0.51 | 0.50 | 0.53 |
| Sodium chlorid, gm. | 6.66 | 2.15 | 7.81 | 9.48 | 6.30 | 4.95 | 7.73 | 9.11 | 12.73 | 12.21 | 10.62 | 9.72 | 9.70 |
| Blood: | | | | | | | | | | | | | |
| Urea, mg. in each 100 cc. | 66 | ... | 56 | ... | 46 | ... | ... | ... | ... | 28 | | | |
| Sulphates, mg. in each 100 cc. | 7.73 | ... | ... | ... | 7.95 | ... | ... | ... | ... | 4.15 | | | |

TABLE 4.—THE EFFECT ON METABOLISM OF TREATMENT WITH CORTICAL HORMONE IN THE TENTH CASE OF OUR EXPERIENCE.

| | January. | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 |
| Weight, kg. | 49.50 | 49.20 | 50.80 | 50.80 | 51.00 | ... | 51.00 | 51.20 | 51.20 | 51.80 | 51.80 |
| Cortical hormone, cc. | ... | ... | ... | 15 | 15 | 15 | 15 | | | | |
| Intake of food: | | | | | | | | | | | |
| Total calories | 2700 | 2800 | 2800 | 3000 | 3000 | 3000 | 2600 | 2900 | 3000 | 2300 | 2200 |
| Protein expressed as nitrogen, gm. | 10.40 | 11.20 | 11.20 | 12.00 | 12.00 | 12.00 | 11.20 | 12.00 | 12.00 | 8.80 | 8.00 |
| Basal metabolic rate, per cent | −3 | ... | −6 | ... | −5 | ... | ... | +1 | +3 | ... | −2 |
| Urine for 24 hours: | | | | | | | | | | | |
| Volume, cc. | 900 | 1170 | 1640 | 1950 | 1250 | 1250 | 1050 | Specimen lost. | 1080 | 1260 | 1050 |
| Total nitrogen, gm. | 5.79 | 5.30 | 5.51 | 4.75 | 5.31 | 6.18 | 5.80 | | 6.14 | 5.74 | 5.29 |
| Urea nitrogen, gm. | 4.26 | 3.90 | 3.68 | 3.25 | 3.76 | 4.28 | 4.48 | | 4.63 | 4.41 | 4.13 |
| Ammonia nitrogen, gm. | 0.48 | 0.44 | 0.60 | 0.40 | 0.44 | 0.60 | 0.48 | | 0.47 | 0.35 | 0.23 |
| Total creatinin nitrogen, gm. | 0.38 | 0.33 | 0.36 | 0.31 | 0.32 | 0.37 | 0.37 | | 0.39 | 0.40 | 0.33 |
| Preformed creatinin nitrogen, gm. | 0.35 | 0.32 | 0.35 | 0.30 | 0.32 | 0.37 | 0.36 | | 0.38 | 0.39 | 0.33 |
| Creatin nitrogen, gm. | 0.03 | 0.01 | 0.01 | 0.01 | ... | ... | 0.01 | | 0.01 | 0.01 | |
| Uric acid nitrogen, gm. | 0.09 | 0.09 | 0.12 | 0.12 | 0.11 | 0.10 | 0.11 | | 0.14 | 0.11 | 0.14 |
| Rest nitrogen, gm. | 0.58 | 0.54 | 0.75 | 0.68 | 0.68 | 0.83 | 0.36 | | 0.51 | 0.47 | 0.46 |
| Nitrogen balance, gm. | +3.57 | +4.78 | +4.57 | +6.05 | +5.49 | +4.62 | +4.28 | | +4.66 | +2.18 | +1.91 |
| Total acids, cc. N/10 | 160 | 121 | 208 | 198 | 196 | 243 | 266 | | 362 | 301 | 149 |
| Phosphate, gm. | 0.30 | 0.23 | 0.35 | 0.37 | 0.31 | 0.39 | 0.53 | | 0.83 | 0.68 | 0.50 |
| Sodium chlorid, gm. | 3.58 | 4.85 | 5.64 | 4.68 | 6.88 | 6.15 | 6.32 | | 6.48 | 8.04 | 5.69 |
| Blood: | | | | | | | | | | | |
| Urea, mg. in each 100 cc. | 20 | ... | ... | ... | ... | ... | ... | | ... | ... | 18 |
| Sulphates, mg. in each 100 cc. | 3.20 | ... | ... | ... | ... | ... | ... | | ... | ... | 3.31 |

TABLE 5.—THE EFFECT ON METABOLISM OF TREATMENT WITH CORTICAL HORMONE IN THE TWELFTH CASE OF OUR EXPERIENCE.

| | February. | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 |
| Weight, kg. | 49.30 | 49.70 | 49.70 | 49.90 | 49.80 | 50.20 | 50.80 | 51.50 | 51.90 | 51.70 | 51.70 | 51.70 |
| Cortical extract, cc. | ... | ... | ... | 15 | 15 | 15 | 15 | | | | | |
| Intake of food: | | | | | | | | | | | | |
| Total calories | 1625 | 1600 | 1750 | 1835 | 2385 | 2400 | 2360 | 2350 | 2450 | 2000 | 2450 | 2740 |
| Protein expressed as nitrogen, gm. | 7.20 | 7.20 | 8.00 | 8.00 | 11.20 | 11.20 | 11.20 | 10.40 | 11.20 | 11.20 | 11.20 | 11.20 |
| Basal metabolic rate, per cent | −27 | −30 | −31 | ... | ... | −24 | ... | ... | −21 | ... | ... | −13 |
| Urine for 24 hours: | | | | | | | | | | | | |
| Volume, cc. | 1000 | 1310 | 1850 | 1690 | 1780 | 1590 | 1700 | 1790 | 1850 | 1510 | 1260 | 1250 |
| Total nitrogen, gm. | 8.20 | 9.47 | 8.50 | 8.17 | 8.52 | 6.21 | 6.85 | 7.11 | 5.71 | 6.99 | 7.09 | 7.19 |
| Urea nitrogen, gm. | 6.85 | 7.79 | 6.92 | 6.58 | 7.07 | 5.24 | 5.79 | 5.94 | 4.84 | 5.98 | 5.74 | 6.03 |
| Ammonia nitrogen, gm. | 0.54 | 0.72 | 0.54 | 0.60 | 0.46 | 0.35 | 0.35 | 0.31 | 0.19 | 0.31 | 0.32 | 0.29 |
| Total creatinin nitrogen, gm. | 0.39 | 0.51 | 0.40 | 0.43 | 0.46 | 0.32 | 0.35 | 0.41 | 0.30 | 0.39 | 0.40 | 0.37 |
| Preformed creatinin nitrogen, gm. | 0.38 | 0.49 | 0.38 | 0.43 | 0.43 | 0.31 | 0.34 | 0.40 | 0.29 | 0.37 | 0.39 | 0.36 |
| Creatin nitrogen, gm. | 0.01 | 0.02 | 0.02 | ... | 0.03 | 0.01 | 0.01 | 0.01 | 0.01 | 0.02 | 0.01 | 0.01 |
| Uric acid nitrogen, gm. | 0.14 | 0.17 | 0.16 | 0.16 | 0.18 | 0.14 | 0.14 | 0.15 | 0.12 | 0.15 | 0.15 | 0.17 |
| Rest nitrogen, gm. | 0.28 | 0.32 | 0.48 | 0.40 | 0.35 | 0.15 | 0.22 | 0.30 | 0.26 | 0.39 | 0.48 | 0.33 |
| Nitrogen balance, gm. | −1.72 | −1.99 | −1.30 | −0.97 | +1.56 | +3.87 | +3.23 | +2.25 | +4.37 | +3.09 | +2.99 | +2.89 |
| Total acids, cc. N/10 | 259 | 335 | 335 | 258 | 324 | 356 | 383 | 280 | 166 | 290 | 423 | 349 |
| Phosphate, gm. | 0.47 | 0.47 | 0.44 | 0.42 | 0.34 | 0.29 | 0.31 | 0.32 | 0.26 | 0.37 | 0.45 | 0.42 |
| Sodium chlorid, gm. | 7.16 | 8.91 | 8.80 | 7.16 | 8.58 | 7.22 | 8.29 | 10.49 | 9.26 | 9.05 | 10.36 | 10.48 |
| Blood: | | | | | | | | | | | | |
| Urea, mg. in each 100 cc. | 56 | ... | ... | ... | ... | ... | 22 | ... | 26 | | | |
| Sulphates, mg. in each 100 cc. | 6.64 | ... | ... | ... | ... | ... | 4.34 | ... | 3.52 | | | |

TABLE 6.—THE EFFECT ON METABOLISM OF TREATMENT WITH CORTICAL HORMONE IN THE FOURTEENTH CASE OF OUR EXPERIENCE.

| | February. | | | | | | | | | | | | March. | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 1 | 2 | 3 | 4 | 5 | 6 |
| Weight, kg. | 57.00 | 57.30 | 57.50 | 57.50 | 57.50 | 57.40 | 57.40 | 57.00 | 57.00 | 56.30 | 56.70 | 57.20 | 57.70 | 58.20 | 58.80 | 59.90 | 60.00 | 60.00 |
| Cortical extract, cc. | ... | ... | ... | ... | ... | 10 | 12 | ... | ... | 15 | 15 | 8 | 10 | | | | | |
| Intake of food: | | | | | | | | | | | | | | | | | | |
| Total calories | 2800 | 2800 | 2800 | 2700 | 2700 | 2800 | 2800 | 2800 | 2300 | 2800 | 2750 | 2800 | 3200 | 3000 | 3150 | 3650 | 3650 | 4400 |
| Protein expressed as nitrogen, gm. | 11.20 | 10.40 | 11.20 | 11.20 | 11.20 | 11.20 | 11.20 | 11.20 | 8.80 | 11.20 | 11.20 | 11.20 | 12.80 | 12.80 | 16.00 | 19.40 | 19.40 | 20.00 |
| Basal metabolic rate, per cent | −4 | −7 | −13 | −7 | −13 | ... | −9 | ... | −13 | −13 | ... | −3 | ... | −3 | ... | −9 | ... | −7 |
| Urine for 24 hours: | | | | | | | | | | | | | | | | | | |
| Volume, cc. | 760 | 760 | 1000 | 1050 | 1490 | 1240 | 1200 | 1150 | 700 | 860 | 850 | 1070 | 1510 | 1500 | 1610 | 1690 | 1900 | 2500 |
| Total nitrogen, gm. | 9.25 | 9.25 | 6.42 | 6.30 | 6.00 | 6.03 | 7.36 | 6.98 | 6.14 | 8.80 | 7.80 | 7.74 | 7.77 | 6.66 | 8.29 | 8.44 | 9.11 | 7.91 |
| Urea nitrogen, gm. | 7.68 | 7.68 | 5.12 | 5.05 | 4.46 | 4.76 | 6.17 | 5.80 | 5.19 | 7.66 | 6.74 | 6.33 | 6.29 | 5.15 | 6.69 | 6.73 | 7.30 | 6.53 |
| Ammonia nitrogen, gm. | 0.51 | 0.51 | 0.32 | 0.31 | 0.51 | 0.22 | 0.22 | 0.21 | 0.15 | 0.23 | 0.21 | 0.40 | 0.42 | 0.38 | 0.44 | 0.34 | 0.42 | 0.34 |
| Total creatinin nitrogen, gm. | 0.49 | 0.49 | 0.47 | 0.48 | 0.49 | 0.48 | 0.52 | 0.52 | 0.43 | 0.49 | 0.49 | 0.46 | 0.51 | 0.49 | 0.56 | 0.53 | 0.53 | 0.49 |
| Preformed creatinin nitrogen, gm. | 0.49 | 0.49 | 0.45 | 0.48 | 0.48 | 0.46 | 0.50 | 0.50 | 0.42 | 0.47 | 0.47 | 0.45 | 0.50 | 0.48 | 0.55 | 0.52 | 0.51 | 0.45 |
| Creatin nitrogen, gm. | ... | ... | 0.02 | ... | 0.01 | 0.02 | 0.02 | 0.02 | 0.01 | 0.02 | 0.02 | 0.01 | 0.01 | 0.01 | 0.01 | 0.01 | 0.02 | 0.04 |
| Uric acid nitrogen, gm. | 0.17 | 0.17 | 0.18 | 0.18 | 0.12 | 0.17 | 0.16 | 0.15 | 0.12 | 0.17 | 0.17 | 0.16 | 0.17 | 0.19 | 0.22 | 0.24 | 0.23 | 0.18 |
| Rest nitrogen, gm. | 0.40 | 0.40 | 0.33 | 0.27 | 0.42 | 0.40 | 0.29 | 0.30 | 0.25 | 0.25 | 0.19 | 0.39 | 0.38 | 0.47 | 0.38 | 0.60 | 0.63 | 0.37 |
| Nitrogen balance, gm. | +0.83 | +0.03 | +3.66 | +3.78 | +4.08 | +4.05 | +2.72 | +3.10 | +1.78 | +1.28 | +2.28 | +2.34 | +3.75 | +4.86 | +6.11 | +9.02 | +8.35 | +10.09 |
| Total acids, cc. N/10 | 384 | 384 | 154 | 201 | ... | ... | 202 | 203 | 256 | 378 | 325 | 472 | 249 | 240 | 243 | 199 | 269 | 323 |
| Phosphate, gm. | 0.70 | 0.70 | 0.38 | 0.48 | ... | 0.47 | 0.58 | 0.52 | 0.49 | 0.77 | 0.66 | 0.69 | 0.53 | 0.51 | 0.64 | 0.63 | 0.72 | 0.74 |
| Sodium chlorid, gm. | 8.64 | 8.64 | 11.82 | 10.78 | ... | 10.20 | 11.96 | 11.48 | 7.48 | 9.50 | 5.15 | 5.69 | 7.79 | 6.72 | 10.37 | 12.50 | 18.92 | 11.15 |
| Blood: | | | | | | | | | | | | | | | | | | |
| Urea, mg. in each 100 cc. | 32 | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | 22 | | | | |
| Sulphates, mg. in each 100 cc. | 3.20 | | | | | | | | | | | | | | | | | |

The effect of treatment with the cortical hormone in increasing appetite and causing gain in weight has been stressed by Rowntree, Greene, Ball, Swingle and Pfiffner. This is well shown in the figures for intake of food in Tables 3, 5 and 6. The initial nitrogen balance in this group of patients apparently varied with the status of the weight curve at the onset of the experiment; it was positive in the 2 cases in which the patients were gaining weight and was in equilibrium or negative in the cases in which the weight was constant or falling. The majority of patients gain weight as a result of this form of treatment. This is accompanied by retention of nitrogen with a corresponding shift in the nitrogen balance. In the 14th case in our experience (Table 6) there was a maximal daily retention of 10.09 gm. of nitrogen. A normal concentration of blood urea at that time indicated that this positive balance was evidence of growth and not of urinary retention. At no time was there evidence of an abnormal or toxic destruction of protein.

**Renal Function.** Numerous observers since the time of Marshall and Davis have called attention to the increase in blood urea and the evidence of renal insufficiency in suprarenalectomized animals. By some this has been considered to be one of the earliest signs of suprarenal insufficiency.

It is recognized that renal insufficiency may be manifest during the critical periods and terminal stages of Addison's disease. It has been our clinical experience that an adequate intake of fluid is necessary in these cases, and that reduction in the latter, sufficient to permit a urinary output of less than 1 liter a day for 2 or 3 days, may be of serious consequence. We have reported evidence of retention of urea in particular during such an episode.

Study of patients with Addison's disease who were in good clinical condition and whose intake of fluid was adequate, for the most part reveals normal values for blood urea and for excretion of phenolsulphonephthalein. The values for urea in each 100 cc. of blood were practically all less than 40 mg. (Fig. 3). Values of more than 50 mg. with a maximal value of 154 mg. were found only if patients were in crisis, vomiting, dehydrated, or who were in collapse or were recovering from this condition. An intensive study of renal function of a patient in crisis is not practicable, and our observations were limited. There is a suggestion, however, that the excretion of phenolsulphonephthalein is reduced at such times. The concentration of creatinin in the blood may be increased when the patient is in crisis; the maximal value observed was 4.8 mg. in each 100 cc. The blood creatinin is a less sensitive index in these cases than is the blood urea and may still be within the normal limits when the latter is considerably elevated. The decrease in the values for blood urea and creatinin in such a case following treatment with the cortical hormone and the supplying of an adequate amount of fluids is shown in Fig. 4. The concentration of uric acid in the

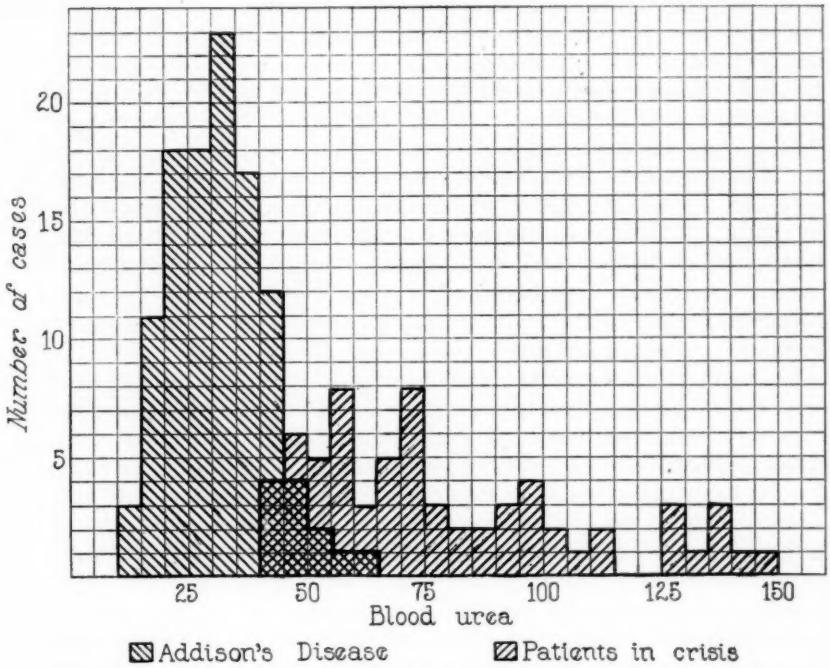


FIG. 3.—The frequency of distribution of the concentration of urea in the blood in a series of cases of Addison's disease. Cases in which the concentration of urea was 40 mg. in each 100 cc. of blood, or more, and in which the patient was in crisis or was recovering from crisis, are marked.

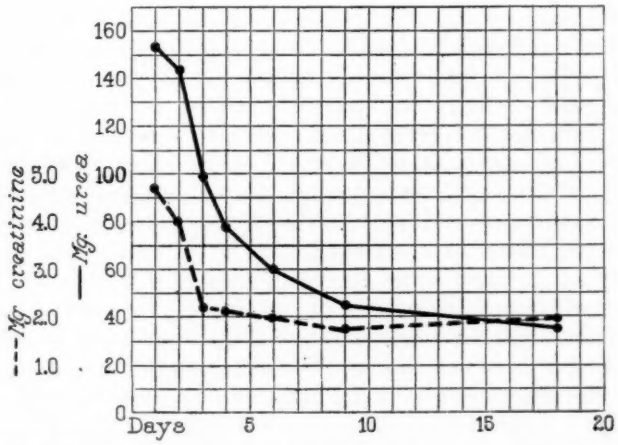


FIG. 4 —The change in the concentration of blood urea and of creatinin, in consequence of treatment of a patient with Addison's disease who was in crisis. Ten cubic centimeters of the suprarenal cortical hormone were given daily during the first week, and the daily intake of fluid was 2000 cc. or more during the period of observation.

blood has been recommended as an index of renal insufficiency, but it did not depart from normal in this group of patients. Wakefield has pointed out the significance of an increase in the sulphates of the serum as an early sign of renal insufficiency. In Addison's disease he found the concentration of sulphates to be normal except during the critical periods and terminal stages of the disease. We are able to confirm this observation. The maximal value obtained was 13.5 mg. in each 100 cc. Occasionally, the value for sulphates in the serum is slightly increased in a case in which the value for blood urea is normal and in which the patient is in fairly good clinical condition. This may well be an incidental observation, for it has been our experience that although there is retention of urea, creatinin and sulphates in the blood of a patient in crisis, and that a period of increased intake of fluid, with diuresis, will dispel this retention, the sulphates are the last to be eliminated and the slowest to return to normal. We have also observed 1 patient who died from Addison's disease, whose blood urea and sulphates were kept within a normal range by means of forced administration of fluids. These results we believe indicate that renal insufficiency in Addison's disease is a secondary manifestation, dependent primarily on such factors as dehydration and circulatory collapse rather than being a direct manifestation of suprarenal insufficiency.

Other elements may enter into this response. Rowntree and Rosenow have both called attention to the delay in the excretion of water by these patients, and a change in the water balance may predispose to anhydremia. However, the fundamental relations we believe are those outlined.

**Carbohydrate Metabolism.** *Blood Sugar.* There has been much discussion of the relationship between the suprarenal glands and the metabolism of carbohydrates. Most of this discussion has been concerned primarily with the part played by epinephrin in physiologic processes. Porges was the first to report decreased values for blood sugar in Addison's disease. The early reports were contradictory. They have been summarized by Rosenow and Jaguttes, who pointed out that hypoglycemia was a frequent but not a constant occurrence. More recent reports have been those of Lawrence and Rowe, Rowntree and Snell, and Chapman.

A study of patients with Addison's disease disclosed that the fasting blood sugar, determined by the Folin-Wu method, varies between 70 and 130 mg. in each 100 cc. with the value in the majority of the cases between 70 and 105 mg., and the peak of the distribution curve between 85 and 90 mg. Values below 70 mg. were found only if patients were in crisis, and we have seen 12 cases in which the readings of blood sugar were between 45 and 70 mg. This degree of hypoglycemia does not necessarily accompany the state of crisis, and normal values for blood sugar may be present at the time of crisis. We agree with Wadi in considering that

hypoglycemia is essentially a phenomenon of collapse. Symptoms suggestive of this condition have been observed by us, but are much confused with the preëxisting evidences of circulatory failure, coma and collapse. In such cases, gradual increase in the fasting blood sugar has been associated with recovery following treatment.

The slight reduction in the fasting blood sugar seen in cases of Addison's disease may be an expression of the anorexia and poor nutritional state which is characteristic of this disease. If, as suggested by others, it represents a characteristic and fundamental disturbance in carbohydrate metabolism, this must be of a special type unrelated to that seen in diabetes mellitus, for we have seen 2 cases, reported by Allan, in which the two diseases were coëxistent.

*Lactic Acid.* The metabolism of lactic acid is closely related to that of carbohydrates. The lactic acid content of the blood of 4 patients with Addison's disease varied between 5.1 and 11.3 mg. in each 100 cc. These are within the usual normal limits, although they come within the lower portion of the latter. Hastings and Compere reported a decrease in the lactic acid content of the blood of suprarenalectomized dogs, although this observation was not confirmed by the studies of Harrop, Pfiffner, Weinstein and Swingle.

**Further Study of the Chemical Condition of the Blood.** Some of the changes in the chemical composition of the blood in Addison's disease have been considered previously (Table 7). Various other changes have been reported in animals following suprarenalectomy. The values for total solids, protein, calcium and potassium are increased, and those for chlorids are decreased. Uncompensated acidosis, with changes in hydrogen-ion concentration, carbon dioxid tension, and carbon dioxid combining power also have been reported. We can confirm the presence of similar changes in clinical cases but again find that the severity of the disturbance varies with the stage of the disease (Table 5). The concentration of serum proteins varies from 5.0 to 7.9 mg. in each 100 cc. among patients who are in good condition. Values between 8.3 and 9.9 mg. were found at the time of crisis. The values for calcium were normal in the cases of the first group, but they varied between 11.6 and 13.5 mg. in each 100 cc. of blood in the cases in crisis. The values for potassium were similarly changed, but these changes were not as striking as those reported in dogs by Hastings and Compere. These observers reported increases much greater than could be explained by the concentration of the blood. The changes in the serum protein and calcium observed in cases of Addison's disease are characteristic of dehydration, or anhydremia, with concentration of the blood. Direct evidence of anhydremia during crisis has also been presented by Rowntree and Brown, who found the blood volume and plasma volume reduced at such times, although normal values were the rule when the patient was in good condition. Changes in the blood which are consequent on dehydration and concentration

TABLE 7.—THE CHEMICAL COMPOSITION OF THE BLOOD OF PATIENTS WITH ADDISON'S DISEASE.

| Serum protein, mg. in each 100 cc. | | Serum calcium, mg. in each 100 cc. | | Serum potassium, mg. in each 100 cc. | | Serum inorganic sulphate, mg. in each 100 cc. | | Serum chlorids, mg. in each 100 cc. | | Carbon dioxid combining power, cc. in each 100 cc. plasma. | | Lactic acid, mg. in each 100 cc. | Blood sugar, mg. in each 100 cc. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| In chronicity. | In crisis. | In chronicity. | In crisis. | In chronicity. | In crisis. | In chronicity. | In crisis.* | In chronicity.* | In crisis.* | In chronicity.* | In crisis.* | In chronicity. | In crisis.* |
| 6.3 | 8.3 | 10.8 | 11.8 | 16.3 | 25.2 | 4.9 | 6.7 | 645 | 565 | 52 | 40 | 9.0 | 70 |
| 7.3 | 9.3 | 10.4 | 11.8 | 19.3 | 28.8 | 3.5 | 6.4 | 575 | 540 | 48 | 30 | 11.3 | 90 |
| 7.9 | 9.9 | 10.8 | 11.6 | 17.8 | 33.3 | 3.2 | 6.6 | 605 | 445 | 60 | 48 | 5.9 | 105 |
| 5.7 | 8.3 | 10.2 | 12.4 | 17.9 | ... | 3.3 | 7.7 | 579 | 540 | 58 | 44 | 5.1 | 50 |
| 5.0 | ... | 10.5 | 13.5 | 24.2 | ... | 4.3 | 8.0 | 620 | 569 | 48 | 47 | 11.7 | 50 |
| 7.1 | ... | 9.4 | ... | 20.1 | ... | 3.5 | 10.5 | 578 | 300 | 45 | 54 | 14.2 | 45 |
| 6.8 | ... | 10.0 | ... | 24.0 | ... | 3.2 | 13.3 | 694 | 495 | 55 | 56 | ... | 43 |
| | | | | | | 4.1 | 7.8 | 651 | 535 | 52 | 35 | ... | 58 |
| | | | | | | | 10.1 | 594 | 528 | 41 | 46 | ... | 67 |
| | | | | | | | 11.7 | 519 | 536 | 68 | 36 | ... | 85 |

* Ten cases taken at random; complete data not given.

must be considered secondary and not direct results of suprarenal insufficiency.

The values for serum chlorids may be low in Addison's disease, although not markedly so, for we find a variation of between 519 and 711 mg. in each 100 cc. Certainly the values are not greatly different from the usually accepted figures for the normal. Lower values occur when the patient is in crisis, 445 to 569 mg. Anorexia and vomiting are both pronounced at the latter time, and the combined effects of reduced intake of salt and loss of chlorids in the gastric content may well account for this reduction. We have previously pointed out that urinalysis did not indicate any great disturbance of the acid-base balance of patients with Addison's disease. The carbon-dioxid combining power of the blood has varied between 41 and 68 volumes per cent of plasma in such cases. Some, but not all, patients who were in crisis gave evidence of acidosis. The range of variation of the carbon dioxid combining power in this group was between 30 and 50 by volumes per cent. The retention of sulphates and of acids in consequence of renal insufficiency has been considered, and such retention may be a factor in producing acidosis. We have recently seen a patient in the terminal stages of Addison's disease to whom it was possible to administer sufficient fluids to insure adequate renal function and to maintain the blood urea and sulphates at normal levels. She was unable to take food, and after several days of virtual starvation the carbon dioxid combining power fell to 15 volumes per cent, while large amounts of acetone and diacetic acid appeared in the urine. Considerable reduction in the degree of acidosis occurred in consequence of intravenous administration of glucose. The acidosis of this patient was due primarily to the ketosis of starvation. These results correspond in great part to those reported by Marañon. They suggest that although patients with Addison's disease as well as suprarenalectomized dogs show disturbances in the acid-base equilibrium, these changes apparently are secondary and are not to be considered as primary manifestations of suprarenal insufficiency. Cholesterol and the blood lipoids were also studied in a few cases, but the results were not greatly changed from normal.

**Acidity of Gastric Content.** Although gastrointestinal disturbances and epigastric pain, suggestive of hyperacidity, are common in Addison's disease, hyperacidity is only occasionally demonstrable by analysis of gastric content. Achlorhydria was present in approximately half of the cases studied, and subacidity in another fourth of them. Analysis of gastric content has not been done as a routine on patients under treatment. There is no change in some cases. On the other hand, one patient with complete achlorhydria to the ordinary Ewald test meal was found to have a free acid of 34 and a total acidity of 50 (in terms of cubic centimeters of 0.1 normal sodium hydroxid) after completion of a course of treatment with cortical hormone.

**Comment.** These results demonstrate the many points of similarity between the chemical and metabolic changes observed in cases of Addison's disease and those reported in suprarenalectomized animals. They also reveal that in the study of these changes the clinical condition of the patient must be considered carefully to exclude the influence of secondary effects not solely ascribable to suprarenal insufficiency.

The patients with Addison's disease in the group studied who were suffering from muscular weakness and asthenia, pigmentation of the skin, anorexia, and loss of weight, but who were otherwise in good clinical condition and were not vomiting or were not dehydrated, had few metabolic abnormalities. The basal metabolic rate usually was slightly reduced. Gastric achlorhydria was common, creatinuria was sometimes present, and the level of fasting blood sugar was slightly reduced. If the patient was losing weight the nitrogen balance was negative. These changes may in part be an expression of the poor nutritive condition of the patient as well as an expression of suprarenal insufficiency.

During a period of crisis, with vomiting, dehydration and circulatory collapse, the effects of anhydremia and renal insufficiency dominate the metabolic picture. The blood volume is reduced; the values for serum protein, calcium and potassium are increased. There is retention of urea, creatinin, sulphates and acid products in the serum; this last may result in a moderate degree of acidosis, although ketosis from starvation may also be a factor in the production of acidosis. Hypoglycemia may be a terminal event. The effects of anhydremia and renal insufficiency may be prevented or eliminated by the administration of adequate amounts of fluid, without preventing a fatal termination of the disease. Usually provision of an adequate supply of fluids has a favorable influence on the clinical course of the disease.

The therapeutic use of the cortical hormone, as we have pointed out, reduces nausea and allays vomiting in the crisis of Addison's disease, and therefore greatly facilitates the administration of adequate amounts of fluids. Under these conditions the evidences of anhydremia and renal insufficiency disappear rapidly. With continued improvement patients gain in weight, the nitrogen balance becomes positive, creatinuria disappears, and the metabolic rate often returns to normal, although this last may be in part only an expression of the improvement in the general state of nutrition.

The paucity, in Addison's disease, of chemical and metabolic changes which can be ascribed solely to suprarenal insufficiency, is significant. Experience with the preparation for therapeutic use of other hormones, such as insulin, pituitary extract, or the parathyroid hormone, which cannot as yet be identified by precise chemical means, has emphasized the importance of rapid and accurate methods of standardizing the activity of commercial preparations. The ability of the cortical hormone indefinitely to

prolong the life of bilaterally suprarenalectomized cats was the measure of its efficiency originally used by Swingle and Pfiffner. Other biochemical methods of standardizing this or similar preparations have since been suggested as being simpler and more rapid, but their validity remains to be demonstrated.

**Summary.** A study has been made of the chemical and metabolic changes observed in cases of Addison's disease, and the effect on these changes of treatment with the cortical hormone of the suprarenal gland.

It is emphasized that the clinical course of a case of Addison's disease may arbitrarily be divided into three stages: (1) The stage of initial destruction of the suprarenal glands; (2) the stage of the recognizable clinical syndrome, and (3) the terminal stage or crisis.

Usually the disease is not recognized until the second stage is reached. At this time there may be loss of weight, asthenia and definite undernutrition. The basal metabolic rate is reduced slightly and there is some reduction in the blood sugar. Such changes become less with treatment, and more marked in the periods of crisis.

The quantities of the various constituents of the urine in Addison's disease corresponded to the lower levels of the usually accepted normal standards. Creatinuria was present in a considerable proportion of cases. Retention of practically all urinary constituents was noted in one case in the course of a period of diminished urinary output. The nitrogen balance of those patients who were losing weight was negative. The majority of patients gained weight as a result of treatment with the suprarenal cortical hormone. In such cases the nitrogen balance became markedly positive.

The period of crisis was characterized by gastrointestinal upsets, nausea and vomiting, pains, circulatory collapse, low blood pressure, dehydration and renal insufficiency. The effect of the last two dominated the chemical picture at this time.

The relation between the chemical and metabolic changes observed in cases of Addison's disease, and those reported in suprarenalectomized animals, and the use of these changes for the standardization of preparations of the suprarenal cortical hormone are considered.

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## ENTERAL ADMINISTRATION OF INSULIN TO NORMAL DOGS.*

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Considerable data have been published that deal with the absorption of insulin by the alimentary tract. Stammers' review of the records, however, shows that insulin administered in this way is ineffective. Usually the failure of oral or enteral administration of insulin has been attributed to its destruction by pepsin or trypsin, and numerous attempts have been made to inhibit the action of these enzymes. Murlin, Sutter, Allen and Piper found evidence of the utilization of sugar in cases of diabetes after insulin in crude solution containing 0.1 per cent hydrochloric acid, had been instilled directly into the duodenum. They also found that insulin in enteric-coated tablets sometimes passed through the stomach and survived the action of trypsin long enough to produce improvement of the diabetes. Peskind, Rogoff and Stewart found that insulin in serum, defibrinated blood, or water was absorbed from the rectum of rabbits, but relatively large doses were necessary, and the effect on blood sugar was more transitory than when smaller doses were given subcutaneously. Administration of insulin by rectum in a solution of sodium chlorid, water or serum, did not affect normal or depancreatized dogs.

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Gaebler and Murlin, working with dogs with phlorhizin diabetes, observed that insulin administered orally, in enteric-coated tablets, combined with malic acid, sodium oleate, and an amino-acid which liberated hydrochloric acid, also administered in solution in blood serum, caused positive, although moderate, reduction of sugar in the urine and increase in the respiratory quotient, and spared protein. The effect was much less than that produced by subcutaneous administration. Similar results with depancreatized dogs were obtained by Murlin and Hawley, who proved that if insulin were protected by blood serum from proteolytic destruction by digestive enzymes, it could be absorbed in significant amounts by the alimentary tract. In some instances the respiratory quotient was raised as high as the value following subcutaneous injection. In several instances the urine was entirely freed of sugar, although the dog was taking a full diet containing meat. The effect on the blood sugar was not as sudden or as great as when insulin is given subcutaneously. The liver seemed to protect the body against the severe effects of a sudden access of insulin to the general circulation. Hypoglycemic symptoms have never been observed following enteral administration of insulin even in huge doses. Four of Murlin and Hawley's dogs were kept alive 81, 125, 41 and 91 days, respectively, after complete pancreatectomy, and while they were on full diets.

Most of the effects of oral or enteral administration of insulin to normal animals have been entirely negative.[1,11] Administration of insulin by rectum to rabbits fails, according to Senstrom, because it is inactivated by the feces. Supniewski, Ishkawa and Geiling have expressed the belief that the large size of the insulin molecule prevents its passage into the circulation when it is injected into the cerebellar cistern. Subcutaneous injections of insulin produced marked decreases in the sugar of the blood and spinal fluid of dogs and rabbits, but intraspinal injection was without effect.

We have used dogs with permanent fistulas at different levels of the gastrointestinal tract so that solutions could be instilled directly or material withdrawn at the desired level. It would appear that direct instillation should avoid the possibility of destruction by enzymes at other intestinal levels. The results were all uniformly negative; as far as could be demonstrated there was not any marked effect on the concentration of sugar in the blood. Control experiments demonstrated that small amounts of insulin absorbed in the portal circulation produced definite decrease in the sugar of the blood. Since these experiments seemed to indicate that effective amounts of insulin did not pass through the normal intestinal mucosa we believed that they might be of some interest.

**Experimental Procedures.** The intestinal fistulas were made by a method of Mann and Bollman which permits ready and frequent passage of a small catheter through a small, exposed segment of intestine, directly into the portion of intestine to which this segment

is anastomosed. Large amounts of solutions thus can be injected directly into the intestine, and in our experiments there was no leakage of injected material. Other animals were prepared so that there were isolated intestinal loops. The loop isolated was about 30 cm. of ileum taken about 75 cm. from the distal end of the ileum and the upper and lower ends were left in the upper and lower ends of the abdominal wound to drain externally. The insulin used was Iletin (insulin–Lilly) U20 or U80 of tested potency. Of the former, each cubic centimeter contains 20 units; of the latter, each cubic centimeter contains 80 units. The concentration of sugar in the blood was determined by the method of Folin and Wu, and specimens of blood were obtained by direct puncture of the jugular vein.

*Administration by Duodenum.* The dog used for these experiments had been prepared 8 months previously, and was in excellent condition, weighing 11.2 kg. The animal had been maintained on the kennel diet and was fasted for 18 hours prior to each experiment. Determinations of blood sugar were made just prior to the administration of insulin, and at intervals of 30 minutes thereafter for at least 3 hours, and in most experiments for 6 hours. The insulin was injected directly into the duodenum through a small catheter as follows: (1) 200 units of insulin in a volume of 10 cc., washed in with an equal volume of water; (2) 200 units of insulin in a volume of 10 cc., mixed immediately before injection with 20 cc. of 0.2 per cent solution of hydrochloric acid; (3) 200 units of insulin in a volume of 10 cc. 1 minute after injection of 10 cc. of 0.2 per cent solution of hydrochloric acid and followed by a similar injection of acid after 3 minutes; (4) 200 units of insulin mixed with 100 cc. of normal dog serum, and (5) 200 units of insulin mixed with 100 cc. of citrated normal dog blood. The determinations of blood sugar need not be given in detail since none deviated from the normal values previously determined for the dog concerned. Injection by the foregoing methods of larger amounts of more concentrated insulin, 400 to 800 units of insulin, of which each cubic centimeter contained 80 units, produced definite lowering of sugar of the blood. Within 30 minutes the concentration of blood sugar was reduced from 40 to 50 mg. for each 100 cc. and returned to normal in from 1 to 4 hours. Symptoms of hypoglycemia were not produced.

*Administration by Jejunum.* This dog had been prepared 2 months previous to the experiment. A catheter passed through the exposed loop of intestine entered the jejunum 20 cm. below the ligament of Treitz. The animal was in good condition and weighed 4.5 kg. The animal had been on the standard kennel diet and was fasted 18 hours prior to each experiment. The insulin was injected directly into the jejunum as follows: (1) 100 units of insulin in a volume of 5 cc., washed in with an equal volume of water; (2) 100 units of insulin mixed immediately before injection with 10 cc. of 0.2 per cent solution of hydrochloric acid; (3) 100 units of

insulin together with 50 cc. of normal dog serum, and (4) 100 units of insulin together with 50 cc. of citrated normal dog blood. Determination of blood sugar taken at intervals of 30 minutes for at least 3 hours after administration of insulin did not disclose deviation from the normal values for blood sugar previously obtained in the animal. Injections of larger amounts of more concentrated insulin were effective in reducing the sugar of the blood to about the same extent as when the insulin was injected into the duodenum.

*Administration by Ileum.* This dog had been prepared 8 months previous to the experiment. A catheter passed through the exposed loop of intestine entered the ileum about 70 cm. from the cecum. The animal was in good condition and weighed 11.2 kg. It had been maintained on the standard kennel diet and was fasted 18 hours previous to each experiment. The insulin was injected directly into the ileum as follows: (1) 200 units of insulin in a volume of 10 cc. washed in with an equal volume of water; (2) 200 units of insulin in a volume of 10 cc., preceded by and followed by injection of 10 cc. of 0.2 per cent solution of hydrochloric acid; (3) 200 units of insulin in a volume of 10 cc., mixed immediately before injection with 20 cc. of 0.2 per cent solution of hydrochloric acid; (4) 200 units of insulin in a volume of 10 cc., together with 100 cc. of normal dog serum; (5) 200 units of insulin in a volume of 10 cc., together with 100 cc. of citrated normal dog blood, and (6) 200 units of insulin in a volume of 10 cc. together with 20 cc. of bile from the gall bladders of normal dogs. Determinations of the blood sugar, made every 30 minutes for at least 3 hours after administration of insulin, did not show appreciable deviation from the normal values previously obtained in the animal. The administration of insulin with blood serum and with blood were all complicated by the fact that the animal began to pass the injected blood or serum by rectum 1 hour and 15 minutes after administration, and in every experiment some blood or serum was passed within 2 hours after administration. Injections of larger amounts of more concentrated insulin were effective in reducing the sugar of the blood, but were less effective than duodenal injections of the same amount.

*Administration by Isolated Ileac Loop.* One dog used in this experiment had been prepared 4 years previously. In dogs with isolated ileac loops of only a few weeks' duration results were similar. The isolated loop consisted of about 30 cm. of ileum, both ends of which were open on the surface of the abdominal wall. The animal was in good condition, weighing 17.4 kg.; it had been fasted for 18 hours. Insulin was slowly instilled into the proximal end of the isolated loop, so that no leakage occurred; 30 minutes were taken for each injection. One hundred units of insulin in a volume of 5 cc. were instilled under the following conditions: (1) Without previous washing of the isolated loop; (2) following washing of the isolated loop with 50 cc. of water; (3) following washing of the loop

with 50 cc. of 0.1 per cent solution of hydrochloric acid; (4) following addition of strong hydrochloric acid to the insulin, so that the solution contained 0.2 per cent of hydrochloric acid, and (5) after addition of 2 cc. of bile from the gall bladder. All of these experiments were satisfactory except the administration with bile. This stimulated secretion in the loop so that the volume increased rapidly, and considerable of the solution was expelled. Determinations of blood sugar taken at intervals of 30 minutes after administration of insulin were all within normal limits. Only one experiment might be regarded as doubtfully significant. After the loop had been washed with 50 cc. of water, 100 units of insulin in a volume of 5 cc. were instilled into the loop in 25 minutes. The concentration of blood sugar before insulin was administered was 108 mg. in each 100 cc., and the readings at intervals of 30 minutes thereafter were 98, 78, 108, 99, 98, 91, 98, 91 mg. Repetition of this experiment did not alter the blood sugar even to this extent, and repeated instillations of 100 units of insulin every 30 minutes for 2 hours was ineffective. Insulin in more concentrated solution caused definite lowering of the sugar of the blood, but symptoms of hypoglycemia were not produced.

The following experiment also was performed on a dog with an isolated intestinal loop. It demonstrates the effect of insulin absorbed into the mesenteric veins. Seventeen and five-tenths units of insulin were injected through a fine needle submucously into the exposed ends of the intestinal loop. Not more than 2 units were injected at one time, and 25 minutes elapsed during the injections. Some leakage occurred at the sites of injection so that the amount actually injected was less than 17.5 units. The concentration of blood sugar was 116 mg. in each 100 cc. when the injections were begun. Five minutes after completion of injections the concentration of blood sugar was 63 mg.; 50 minutes after injection, 51 mg.; 1 hour and 20 minutes after injection, 44 mg.; 1 hour and 50 minutes after injection, 46 mg.; 2 hours and 50 minutes after injection, 62 mg., and 3 hours and 50 minutes after injection, 86 mg.

That the mucosa of the isolated loop was not completely impervious to substances in solution was demonstrated by the following experiment: 6 mg. of phenolsulphonephthalein, in a volume of 1 cc., was instilled into the proximal end of the isolated intestinal loop. One hour later the urine contained 30 per cent of the injected phenolsulphonephthalein and in the next hour 10 per cent was recovered. At the end of this period the mucosa of the isolated loop was still deeply stained.

That insulin does disappear from the contents of an isolated ileac loop is shown by the following experiment: After preliminary washing of the isolated ileac loop with water, 100 units of insulin in a volume of 5 cc. were instilled into the loop. One hour later

the loop was washed twice with 5 cc. of water; the entire volume of water was recovered. No change was produced in the sugar of the blood of this animal. The insulin from the ileac loop, washed out after 1 hour, was then injected subcutaneously into a dog weighing 5.1 kg. The sugar of the blood at the time of injection was 85 mg. in each 100 cc. and at intervals of 30 minutes afterward was 74, 47, 52, 54, 72, 84, and 86 mg. in each 100 cc. Thus it is seen that sufficient insulin remains after having been 1 hour in the loop to produce a definite decrease in the blood sugar of an animal after subcutaneous injection. It is clear, also, that about 90 per cent of the insulin instilled in the intestinal loop had disappeared within an hour.

If destruction of insulin was caused by enzymes within the lumen of this portion of bowel, it was considered that comparable destruction should occur if the washings of this loop were incubated with insulin. One hundred units of insulin in a volume of 5 cc. were instilled into an isolated ileac loop which had not been washed for several days. Five minutes later this was washed out with 6 cc. of water; a small portion of the washings was unavoidably lost. The entire volume of recovered fluid was 6 cc., which was incubated at 37° C. for 1 hour and 30 minutes. The entire solution was then injected subcutaneously into a dog weighing 6.6 kg. At the time of injection the blood sugar was 83 mg. in each 100 cc. and at intervals of 30 minutes following it was 65, 58, 52, 52, 50 and 45 mg. at which time hypoglycemic convulsions occurred. The animal recovered immediately after intravenous injection of 15 gm. of glucose but later died of hypoglycemia. This experiment indicates that little enzymatic substance capable of rapidly destroying insulin is present within the isolated ileum.

**Comment.** Experiments on animals with a loop of ileum isolated from the remaining portions of the gastrointestinal tract failed to show evidence of effective absorption of insulin, but these experiments appear to be more instructive. With the demonstration that insulin injected submucously in the ileum is of approximately similar effect to that injected subcutaneously in producing decrease in the sugar of the blood, it would appear that any appreciable absorption from the mucosa, or unaltered insulin, would likewise decrease the sugar of the blood. Since washings from the loop of ileum 1 hour after instillation of insulin produced definite lowering of the concentration of glucose in the blood of dogs following subcutaneous injection of these washings, one is justified in assuming that all of the insulin was not destroyed within the loop. From a quantitative standpoint it appears that about 90 per cent of the insulin instilled in the loop of ileum disappears within an hour. The sugar of the blood was not altered by the large amount of insulin that disappeared. It must have been destroyed either within the lumen of the intestine or within the mucosa. If enzymes secreted into the

lumen of the bowel destroyed insulin rapidly, washings from this portion of the intestine should destroy insulin when incubated with it. Experiments showed that insulin was not rapidly destroyed by incubation after having been washed through a portion of the ileum. It would appear that insulin is destroyed by the mucosa of the intestine. The effectiveness of concentrated insulin appears as evidence that the intestine is not impervious to this substance, and also indicates that the inactivation of insulin by the mucosa of the intestine may be incomplete if absorption is sufficiently rapid.

From the work of Fisher, and Fisher and Noble, one might possibly conclude that the insulin is not destroyed by the intestine but that it may be inactivated and excreted by the kidneys. They found that insulin administered by a Thiry fistula lowered the blood sugar of depancreatized dogs and of normal puppies, but that it was without effect on normal dogs. Large amounts of insulin were recovered in the urine following the enteral administration of insulin to normal and to diabetic dogs.

It should be emphasized that in all of our experiments normal dogs were used and that any conclusions concerning the action of the intestine on insulin must necessarily refer only to normal tissues. It is possible that in pathologic conditions such as diabetes, alterations in the permeability of various tissues may be present.

**Summary.** Large amounts of insulin may be instilled directly into the duodenum, jejunum or ileum without any appreciable effect on the sugar of the blood of normal dogs, except for the slight effects when concentrated insulin was used. The addition of acid, blood, or bile to insulin thus administered did not alter this. If insulin is injected into the lumen of an isolated portion of ileum the blood sugar of the animal is not affected, but small amounts of insulin given submucously produce typical hypoglycemia. Insulin gradually disappears from within the lumen of the ileum. With the doses we have used, sufficient insulin remains after 1 hour to produce definite hypoglycemia if injected subcutaneously. Insulin incubated with ileac washings is not so rapidly destroyed. It would appear that the intestinal mucosa inactivates insulin so that it is not effectively absorbed. Small amounts of insulin may escape inactivation if sufficiently concentrated insulin is applied to the intestine.

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## THE ELECTROCARDIOGRAPHIC DIAGNOSIS OF CORONARY OCCLUSION BY THE USE OF CHEST LEADS.

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Many cases of coronary occlusion do not show characteristic changes in routine electrocardiogram. It seems that there are "silent areas" in the heart where infarction may occur without producing a deviation of the $S$–$T$ interval from the isoelectric line in any of the three conventional leads. During some recent animal experimentation[1] we found that typical electrocardiographic evidence of cardiac infarction could be recorded after occlusion of arteries supplying hitherto silent areas. To do this it was necessary to depart from the three conventional leads and to lead the cardiac action currents to the galvanometer from new points. Shortly after these experiments were completed a patient presented herself with a clinical picture typical of coronary occlusion, but with no electrocardiographic indications of the presence of such a lesion (Fig. 1-*A*, Leads I, II and III.) We, therefore, departed from the three conventional leads, applied the electrodes to the anterior and posterior surfaces of the chest wall and obtained striking deviations in the $S$–$T$ interval from the isoelectric line. (Fig. 1-*A*, Lead IV.) The results obtained in this case and in another subsequent one (Fig. 2) make it apparent that the anteroposterior chest lead (Lead IV) is an important adjunct to the routine electrocardiogram

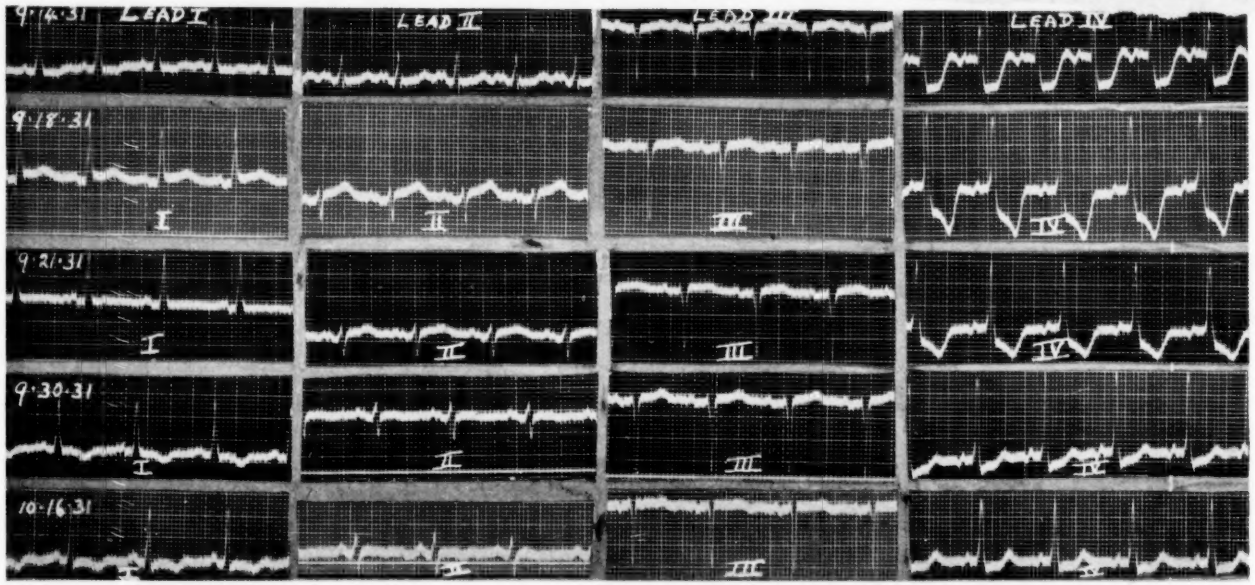


FIG. 1.—Case 1. *A*. Severe attacks of pain had occurred on September 12 and September 14, 1931. This tracing was made shortly after the subsidence of the attack on the latter date. Leads I, II and III do not suggest the presence of a recent myocardial infarct. Lead IV shows an *S–T* interval depression of 6 mm. *B*. Tracing taken September 18, 1931, four days after the last attack of precordial pain. There was still a slight leukocytosis (13,000). The temperature was still somewhat elevated. Lead I shows an *R–T* interval elevation of 1.5 mm. This is the only finding suggestive of coronary occlusion which was found in any single tracing taken with the three conventional leads. Lead IV shows an *S–T* interval depression of 5 mm. and a deeply inverted *T* wave. *C*. Tracing taken, September 21, 1931. The general condition of the patient had improved considerably by this time. There was still a leukocytosis of 11,000. The temperature reaction had practically subsided. The first three leads show no phenomena suggestive of coronary occlusion. Lead IV still shows an *S–T* interval depression of 2.5 mm. and a deeply inverted *T* wave. *D*. Tracing taken, September 30, 1931. The patient was afebrile and had a leukocyte count of 9300. Her general condition had improved markedly. The *T* wave in Lead I is beginning to show inversion. Lead IV still shows a depression of the *S–T* interval. A slight amount of overshooting in this tracing renders measurement of this abnormality inaccurate. The *T* wave in Lead IV is beginning to become upright. *E*. Tracing taken, October 16, 1931. Patient convalescing satisfactorily. Minor changes have appeared in Leads I, II and III. Lead IV shows an *S–T* interval depression of 1 mm. and a definitely upright *T* wave. This latter finding constitutes an abnormality in Lead IV. The progressive changes manifested in these tracings from day to day constitute strong presumptive evidence of coronary occlusion.

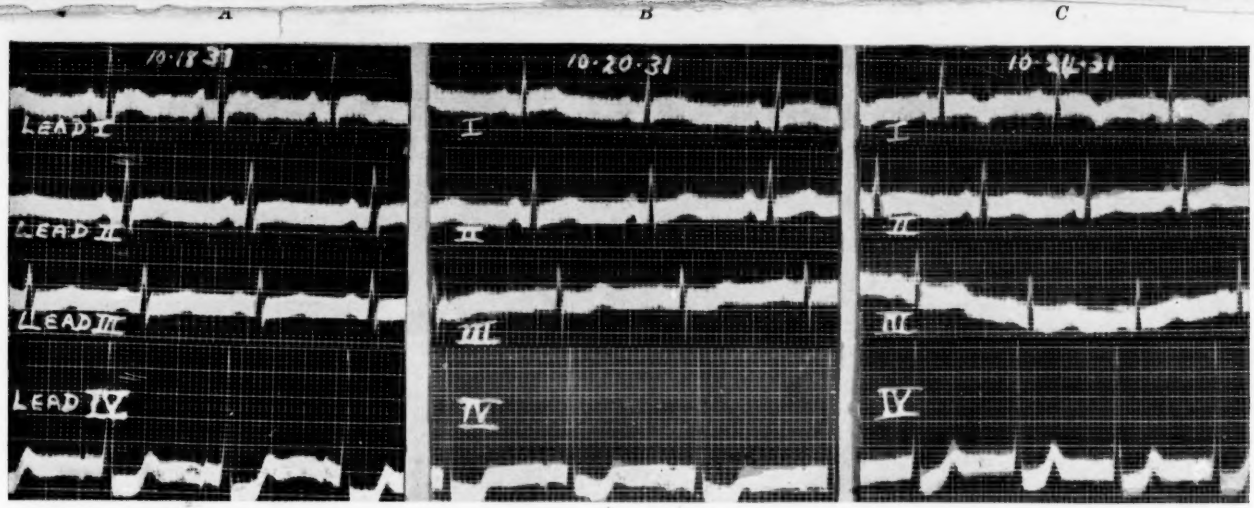


FIG. 2.—Case 2. *A*. Tracing taken, October 18, 1931. Severe attacks of pain had occurred on October 5 and October 8. There had been no definite evidence of an extension of the infarction since the latter date, although there was a fever of 99.3° F. and a leukocytosis of 13,000 when this tracing was taken. The contours of the *R–T* interval and *T* wave in Lead I suggest the diagnosis of coronary occlusion. Lead IV shows an *S–T* interval depression of 3 mm. *B*. Tracing taken, October 20, 1931. The febrile reaction was still present. There is practically no suggestion of coronary occlusion in Leads I, II and III. Lead IV shows an *S–T* interval depression of 2 mm. *C*. Tracing taken, October 24, 1931. The febrile reaction had begun to subside. The leukocyte count was 9000. The *T* wave in Lead I shows beginning inversion. The contours of the *S–T* interval and *T* wave suggest the diagnosis of recent myocardial infarction. Lead IV shows a depression of the *S–T* interval of 3 mm. The progressive changes which have occurred in the contour of the ventricular complex, especially in Lead I, are presumptive evidence of coronary occlusion.

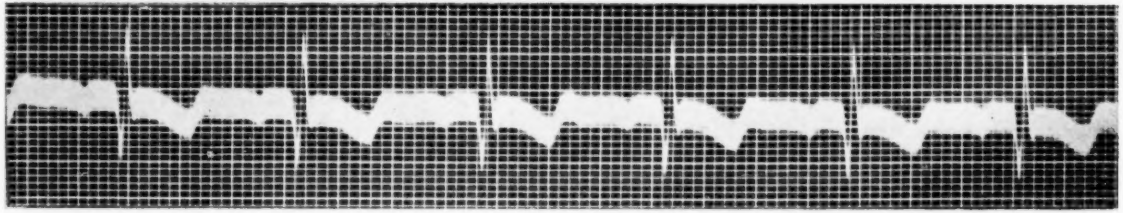

FIG. 3.—The normal contour of Lead IV—the anteroposterior chest lead. The *P* wave is usually inverted, a *Q* wave is

in the diagnosis of certain cases of coronary occlusion. Craib[2] has discussed the "silent areas" in the heart and has outlined the reasons for their failure to affect the electrocardiogram taken from the conventional three leads. Chest leads have been employed by various investigators for many years in the study of the heart. Waller,[3] in his original work with the capillary electrometer, in 1887, placed his electrodes directly on the chest wall. Lewis has used this method repeatedly since 1909,[4] especially in his studies of the mechanism of auricular action. However, so far as we are aware, chest leads have not been employed hitherto for the clinical study of cardiac infarction. Certainly, if they have been, the results are not commonly known.

**Case Reports.** CASE 1.—M. K., a white female, aged 76 years, was admitted to the Hospital of the University of Pennsylvania (Dr. Stengel's service) on September 14, 1931. She had had mild diabetes for at least 7 years, and was known to have had a slight elevation of blood pressure (160 systolic and 90 diastolic) before the onset of the present illness. In other respects her past medical history is irrelevant. She had been enjoying her usual state of health until September 1, 1931, when, while walking on the street, she was seized with a severe paroxysm of pain in the precordium and epigastrium, accompanied by a feeling of suffocation. She collapsed in a nearby drugstore. The attack lasted 20 minutes and then disappeared completely, leaving only a sense of fatigue. A second attack occurred after she had eaten her supper on September 5. It was similar to the first and lasted 10 minutes. On September 12, at 11.30 P.M., when the patient was in bed, a third attack of pain seized her. It was similar in location to the other two, but it was much more severe and lasted for 5 hours. Morphin was required for relief. The blood pressure at that time was 180 systolic and 100 diastolic. A fourth attack occurred at 7 A.M. on the day of admission to the hospital, September 14. It was the most severe of all and lasted until the patient had been quite heavily narcotized with morphin at 11 A.M. A definite soreness of the precordium continued for more than 24 hours.

*Physical examination* on admission showed an elderly white woman with a temperature of 97° F., a pulse rate of 100 and a respiratory rate of 22 per minute. She appeared acutely ill. She was restless and slightly cyanosed. There was an odor of acetone on her breath. There was definite tenderness over the precordium. The heart was not demonstrably enlarged. The cervical veins were not engorged. The heart sounds were regular and of normal intensity. No murmurs were heard. There were crackling râles at the lung bases. The abdomen was distended. The liver was not palpable. There was no edema of the feet or sacrum.

*Diagnosis.* The patient's history and examination suggested the diagnosis of coronary occlusion.

*Course.* This diagnosis was born out by the subsequent course of events: (1) There was a rise of temperature to 101° F. for several days, then a gradual subsidence. (2) The leukocyte count was 16,000 on September 14, 14,000 on September 17 and slowly decreased to 9800 on September 28, 1931. (3) Although there was no acute shock on admission (blood pressure, 155 systolic and 90 diastolic), by the next day, September 15, the pressure had fallen to 110 systolic and 60 diastolic. It then began to rise slowly, reaching 130 systolic and 90 diastolic on September 18, and has fluctuated in that region ever since. (4) A definite friction rub was heard

at the apex on September 16. It disappeared the next day. (5) There was a moderate degree of tachycardia (90 to 110) for several days after admission. The rate subsided to 75 during the course of the next 2 weeks. (6) Definite signs of congestion developed at the lung bases, persisted for 10 days and then cleared up gradually.

The patient's diabetes and acidosis were promptly controlled with glucose, insulin and dietary measures. Dysuria and abdominal distention were troublesome, but finally yielded to treatment. The patient made a tardy recovery. At the present writing, October 25, 1931, she is apparently well on the road to a healing of her infarct but she still remains weak and incapacitated for any exertion.

The *electrocardiographic studies* constitute the center of our interest in this case. Tracings were taken daily from the day of admission, September 14, until September 19, then every other day until October 2, 1931. Since then they have been made at intervals of 4 to 6 days. The three conventional leads were taken with the patient in the semirecumbent position in bed. In addition, a chest lead was used. (This lead has been designated Lead IV for the sake of convenience.) The following method was employed: Pads moistened in warm saline were placed over the front and back of the chest, approximately at the cardiac level, just to the left of the midline. The ordinary German silver electrodes were placed over these pads. The anterior electrode was connected to the right arm lead wire. The posterior electrode was connected to the left arm lead wire. A simple method of holding the electrodes snugly in place was found to be the use of a ⅜-inch rubber tube stretched fairly tightly around the chest over the electrodes and clamped at the ends with a hemostat. It is vital to have the resistance low, and to standardize the string accurately. Overshooting may produce changes in the electrocardiogram of normal individuals, which might be confused with significant $S$–$T$ interval deviations. Rubbing the skin with alcohol, burnishing the electrodes and keeping the pads hot and closely applied to the skin are the main precautions necessary to prevent overshooting.

The following three points are brought out by the tracings (Fig. 1): (1) The progressive changes which took place in Leads I, II and III during the course of the first 4 weeks suggest the diagnosis of coronary occlusion. (2) Of all the 20 tracings taken from time to time by the three conventional leads, no single tracing gave any indication of the presence of a myocardial infarct, except possibly that taken on September 18, 1931. (Fig. 1-*B*.) Even in this tracing the $R$–$T$ interval elevation did not exceed 1.5 mm. (3) Lead IV (the chest lead) gave unmistakable diagnostic information the very first day and continued to do so for 8 days after the infarction. From the eighth to the sixteenth day the evidence was less definite, but certainly suggestive. The marked depression of the $S$–$T$ interval, which was present during the first week subsequently gave place to an upright $T$ wave.

CASE 2.—A business man, aged 62 years, was apparently well until October 3, 1931. That night he had a brief attack of pain in the left side of the neck and precordium. On October 5 at 8.30 P.M., while walking home he was seized with a very severe pain also located in the neck and precordium. He was barely able to reach home. His physician, Dr. C. I. Ulmer, was immediately summoned. The pain persisted for 2 hours despite the prompt administration of morphin. On October 8 the patient had a second severe attack, lasting 2 hours, also requiring morphin for relief. Since then he has had no more actual pain. However, during October 15 and October 16 he was very badly bothered with a great deal of gas in his stomach.

He was first seen by one of us on October 17, 1931. He had a slight fever (99° F.) and a moderate leukocytosis (13,000) until October 24,

His blood pressure was 130 systolic and 70 diastolic. (It had been recorded at 160 systolic a few weeks prior to the present illness.) There was slight cyanosis of the lips and nail beds. The heart sounds were normal and not unduly rapid. There was no pericardial friction, and no evidence of circulatory failure. He had a brief, mild pain in the throat on October 18, somewhat similar to the more severe pains referred to above. Since then he has had no suggestion of cardiac pain.

The *electrocardiographic studies* of this patient are shown in Fig. 2. The following facts are brought out: (1) The progressive changes in the tracing are highly suggestive of a recent coronary occlusion. (2) The appearance in Lead I, when considered in conjunction with the clinical picture, practically establishes the diagnosis of myocardial infarction. (3) As in Case 1, Lead IV shows the most striking electrocardiographic phenomena (a 3-mm. $S$–$T$ interval deviation).*

Thirty-three controls (20 normals and 13 patients with cardiovascular disease) have been studied by means of Lead IV. The normal tracing in this lead is illustrated in Fig. 3. The $P$ wave is often inverted. The $Q$–$R$–$S$ complex is often of higher voltage than that seen in the other three leads. There is usually a deep $T$ wave. The $T$ wave is inverted.† Deviations of the $S$–$T$ interval from the isoelectric line were not seen in this group. We presume that when $S$–$T$ interval deviations appear in Lead IV they probably have the same significance as when they occur in the three conventional leads. That is, they are nearly, but not quite, pathognomonic of myocardial infarction.[5]

**Comment.** Apparently Lead IV will bring to light infarcts in areas hitherto electrocardiographically silent. Probably there are no truly "silent areas" in the heart. An infarct of appreciable dimensions‡ will probably always produce a recordable change in the action current of the heart, no matter where it is situated. The reason why certain parts of the heart muscle do not affect the routine electrocardiogram is probably because the axes of our conventional leads have not been suitably placed to record changes in the action current in these areas.[2] It is possible, therefore, that other chest leads besides Lead IV may occasionally be useful.

It is possible that Lead IV may find a place in routine electrocardiography. It would seem logical to use it, since it appears to give information concerning the condition of parts of the heart muscle which do not produce effects on the routine electrocardiogram which we are able to recognize as significant. In certain of our controls with cardiac damage we found $T$ waves opposite in sign to the normal.

If conclusions are to be drawn from minor daily variations in

* Follow-up examination on November 27, 1931: the $S$–$T$ interval in Lead IV had returned to the isoelectric line; the $T$ wave was +4 mm. Recovery had been uneventful and satisfactory; $T_1$ was −3 mm., $T_2$ was +1.5 mm., $T_3$ was +4 mm.

† An inverted mirror image of this tracing with no $Q$ wave and an upright $T$ wave can be produced by reversing the lead wires.

‡ The exact size of an infarct necessary to produce a detectable change in the electrocardiogram taken from the surface of the body has not been determined.

the contour of the tracing in Lead IV the relation of the electrodes to the heart should be kept constant. We paid no attention to minor variations in the position of the electrodes and have not drawn conclusions on these grounds.

Changes of so-called "specific" nature have been noted in 50 per cent of attacks of angina pectoris.[6] It is possible that the incidence of "specific" changes might be greater if four leads were used instead of three.

Barnes and Whitten[7] have shown that it is often possible to localize a myocardial infarct by means of the electrocardiograph. Lead IV should assist materially in accomplishing this. In the light of the results of our animal experimentation we would expect an anterior infarct to produce an $S-T$ interval depression in Lead IV, whereas a posterior infarct should produce an $R-T$ elevation.* According to this hypothesis, we suspect that both of our patients suffered infarction of the anterior wall of the left ventricle. This suspicion is strengthened by the electrocardiographic phenomena in Leads I, II and III. The expected subsequent development of a $T$ wave of the opposite sign was noted in Case 1. A final evaluation of the usefulness of Lead IV in the localization of myocardial infarcts will necessarily await combined electrocardiographic and necropsy study of a series of cases.

**Summary and Conclusions.** Two cases are reported to illustrate the use of Lead IV (an anteroposterior chest lead) in the electrocardiographic diagnosis of coronary occlusion. In Case 1 the three conventional electrocardiographic leads yielded little or no diagnostic information except on the fourth day. Nevertheless, for 8 days after the original infarction Lead IV showed striking and unmistakable deviation of the $S-T$ interval from the isoelectric line. In Case 2 both Leads I and IV showed evidence of coronary occlusion. Lead IV showed a much more striking $S-T$ interval deviation than was seen in Lead I.

In a series of 33 controls deviation of the $S-T$ interval from the isoelectric line was not seen. When $S-T$ interval deviations appear in Lead IV they probably have the same significance as when they occur in the three conventional leads.

The employment of chest leads adds materially to the usefulness of the electrocardiograph in the study of certain cases of myocardial infarction. When the three conventional leads show no evidence of coronary occlusion, Lead IV may show striking deviations of the $S-T$ interval from the isoelectric line.

It is apparent that certain of the areas of the myocardium which are "silent" in the three conventional leads have a definite effect on Lead IV.

The usefulness of Lead IV in routine electrocardiography and in the location of myocardial infarcts is discussed.

* These statements apply only if the lead wires are attached as specified above.

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## AURICULAR FIBRILLATION.

### ITS ETIOLOGY, AGE INCIDENCE AND PRODUCTION BY DIGITALIS THERAPY.

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HEART failure is associated so frequently with auricular fibrillation that the relationship between the two is now clearly established. The *modus operandi* of this relationship is not, however, clear, and this point, along with certain prognostic considerations, has been the subject of much speculation. Despite a number of excellent statistical reports upon the subject of auricular fibrillation, several important points have not been emphasized. Among the latter can be included the great rarity of auricular fibrillation in the various forms of syphilitic heart disease, the age incidence of the arrhythmia and the production of auricular fibrillation as a result of too enthusiastic administration of digitalis and its products. An attempt will be made in this paper to illustrate these points by a review of the material collected in The Johns Hopkins Hospital.

Since the publication of Mackenzie's[24] original observations many authorities have confirmed the fact that fibrillation of the auricles is almost the rule when a heart, crippled by mitral stenosis, is no longer able to meet the demands of the circulation. It is also known that

auricular fibrillation is rare in disease of the aorta or of the aortic valves. In Lewis'[18] series of 152 cases of auricular fibrillation 51.5 per cent had mitral stenosis and but 5.9 per cent had aortic valvular disease while 46.7 per cent gave a history of rheumatic fever or chorea and but 0.7 per cent had a history of syphilis. In the series of 359 cases reported by Brachman[2] 37 per cent had mitral stenosis, 37 per cent "appeared to be primary myocardial" and 1.4 per cent had aortic disease alone. Cookson's[9] 361 cases, seen at the London Hospital, were distributed as follows: postrheumatic heart disease 69 per cent, nonrheumatic heart disease (including the instances of hypertension and arteriosclerosis) 22 per cent, exophthalmic goiter 7 per cent and syphilitic aortitis 2 per cent.

A study has been made of the records of 575 patients seen here during the past 12 years in whom the electrocardiograms have at one time or another shown auricular fibrillation. This series embraces all the instances of auricular fibrillation recognized among the electrocardiographic records of the hospital during that period.

**Etiology.** From the clinical notes and from the necropsy protocols, when such have been available, the cases have been divided into groups, according to etiology, as indicated in Fig. 1.

Patients with rheumatic heart disease (mitral stenosis alone or in combination with other valvular lesions) constituted the largest single group—forming 34.4 per cent of the total number. The "arteriosclerosis" group, comprising 31.1 per cent of the total, contains those elderly individuals with generalized arteriosclerosis in whom the systolic blood pressures at the time of examination were not above 150 mm. of mercury.* In the "hypertensive" group are included those cases in which the systolic blood pressures were above 150 mm. of mercury (a purely arbitrary figure). In some cases arteriosclerosis or renal disease was also present. Under the heading of "emphysema" are grouped those patients in whom the conspicuous abnormality appeared to be chronic bronchitis, emphysema or fibroid pulmonary changes of long standing. A certain degree of arteriosclerosis was of course present in the majority of the latter cases as they fell in the later decades of life. It is of particular interest that auricular fibrillation was associated with syphilitic cardiovascular disease in but 3 per cent of the total series. This point will be discussed more fully later.

**Age Incidence.** The age incidence of auricular fibrillation corresponds closely to that of myocardial insufficiency resulting from rheumatic and degenerative forms of heart disease. The percentage occurrence in various decades is dependent upon the type of clinical cases encountered, and is, therefore, not strictly comparable in different series. Some authors note the age at onset and others

* Cookson[9] uses the term "nonrheumatic" rather than "arteriosclerotic" to characterize this group. Because of its questionable etiology it has been referred to in the French literature as the "primitive type."

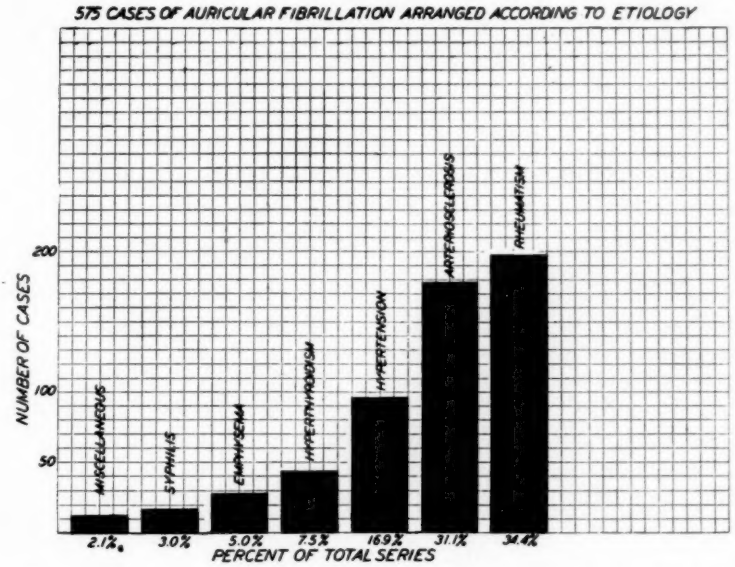


FIG. 1.—Shows the distribution according to etiology of 575 cases of auricular fibrillation.

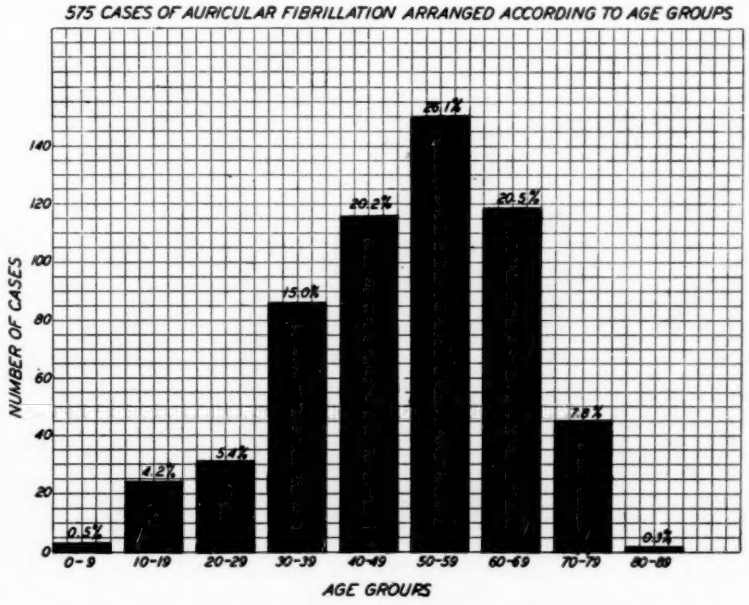


FIG. 2.—Shows the distribution in percentages according to age groups in 575 cases of auricular fibrillation.

the age at which auricular fibrillation was first recognized. In Mackenzie's[22] series of 500 cases of auricular fibrillation the greatest incidence was in the decade from 56 to 66; in Willius'[40] 500 cases, between 51 and 60, and in Cowan and Ritchie's[11] series of 300 cases, between 40 and 49. The incidence of rheumatic heart disease, which tends to cause auricular fibrillation in the earlier decades, is rather high in the latter series. In 78 rheumatic cases recorded by Cookson[9] the onset of auricular fibrillation occurred between the ages of 12 and 17 in almost one-third (23 cases).

In the present series, as will be seen by reference to Fig. 2, the highest incidence of auricular fibrillation was in the decade from 50 to 60.

**Auricular Fibrillation in Childhood.** Considerable interest has centered of late upon the incidence of auricular fibrillation in childhood. Examples of it are scarcely ever seen in the first decade, and the 3 instances in this series are therefore noteworthy. This figure probably represents fairly well the frequency of occurrence of the irregularity in a general hospital. Willius[40] noted no case occurring in the first decade among his 500 cases and Cowan and Ritchie[11] no instance in 300 cases. In 1164 cases of auricular fibrillation at the London Hospital, Cookson[8] found 30 (2.5 per cent) below the age of 17 and added 5 from other sources. In only 10 cases was there proof by graphic records. There was no instance occurring below the age of 12 years. Auricular fibrillation in Nadel's[27] case in a boy of 11 and in Neuhof's[28] case in a boy of 8 was the result of digitalis therapy although rheumatic heart disease was present in each. Two well-authenticated instances of auricular fibrillation occurring in the first decade have been recorded by Leys and Russell,[20] and Sutherland and Coombs[39] respectively; the first in a boy of 6 with questionable diphtheritic myocarditis and the latter in a boy of 5 with acute rheumatic fever. Cookson[8] in 1929 was able to collect from the literature 13 instances in which auricular fibrillation appeared during the first 10 years of life; several of these cases are doubtful. Resnik and Scott[33] have recorded the youngest case of auricular fibrillation in the literature for which there is graphic proof. Their case was in a boy 4 years of age (Case 3 of our series), who had rheumatic heart disease. The other 2 cases are described briefly below.

**Case Reports.**—CASE 1. N. E., female, aged 8 years (H. L. H. 65378), was admitted to the hospital January 3, 1930, and died January 15, 1930. The child was well until the age of 6 when she developed scarlet fever which was followed by a rather severe attack of rheumatic fever and the family was told that the heart was "involved." Because of a general decline in health with weakness, fever, loss of weight and anorexia for a year she was admitted to the hospital. On admission there was slight fever, tachycardia, tachypnea, pallor, undernutrition, an enlarged heart with classical signs of mitral stenosis without signs of congestive heart failure. On the second day after admission without any other change of significance in her general

condition auricular fibrillation set in. She was then digitalized rapidly with a satisfactory drop in pulse rate but without restoration of normal rhythm. Finally a week after the onset, as congestive failure had not developed and as a totally irregular cardiac rhythm persisted, she was given 1 gm. of quinidin in divided doses over 16 hours. The administration of the drug was apparently accompanied by no untoward symptoms until a few minutes before death when the nurse noted that she was groaning and in much discomfort and before the house officer had arrived she died. A postmortem examination was not permitted.

CASE 2.—K. D., male, aged 8 (H. L. H. 57863), was first admitted to the hospital May 18, 1928, and died December 3, 1929. Postmortem examination revealed subacute rheumatic endocarditis involving all the valves and the endocardium of the left auricle, rheumatic myocarditis and chronic passive congestion of the lungs, liver, spleen and kidneys.

Fifteen months before entry he was ill for 3 months with severe rheumatic fever. Five months before entry the rheumatism recurred. On admission there was slight fever, emaciation, pallor, occasional choreiform movements, numerous subcutaneous fibroid nodules and signs over the heart that suggested mitral stenosis and insufficiency without congestive failure. An electrocardiogram revealed normal sinus rhythm. He did not do well but went home for short periods twice before the final admission. A year and a half before death, congestive heart failure became conspicuous and he was digitalized. From then until death heart failure and rheumatic infection progressed slowly. In September, 1929, he was admitted with well-marked heart failure and auricular fibrillation. For months he had been taking only maintenance doses of digitalis. After a week on quinidin the cardiac mechanism reverted to normal and remained so though he slowly grew worse and died December 3, 1929.

CASE 3.—Reported in detail by Resnik and Scott.[33]

Schwartz and Weiss[38] studied 60 consecutive cases of rheumatic heart disease in children between 5 and 15 years of age who had been admitted to the Montefiore Hospital in New York. Auricular fibrillation was found in 10, at one time or another, and 4 of these were below 10 years of age. They maintained that this cardiac irregularity in young children was more frequent than is generally believed, and suggested that careful and continuous observation was necessary in order to recognize it. From the case histories it would seem highly probable that auricular fibrillation was brought on by digitalis in some instances. Certainly few observers would agree that the high incidence in the Montefiore series represented the usual experience.

The following table compiled by Cookson[9] clearly indicates the grave prognosis that is associated with auricular fibrillation in childhood as compared to the later decades.

THE EXPECTATION OF LIFE IN RHEUMATIC CASES WITH FIBRILLATION CLASSIFIED ACCORDING TO AGE OF ONSET. (AFTER COOKSON.)

| Age at onset of fibrillation. | No. of cases. | Duration of life. |
|---|---|---|
| 12 to 17 | 23 | 10.0 months |
| 18 to 28 | 22 | 4.5 years |
| 28 to 38 | 16 | 6.5 years |
| 38 to 48 | 8 | 5.8 years |
| Over 48 | 9 | 4.1 years |

This experience is illustrated in our 3 cases described above in which death occurred 10 days, 3 months and 10 months respectively after the onset of auricular fibrillation.

No attempt is made here to separate the instances of paroxysmal auricular fibrillation from those in which the arrhythmia was permanently established. Such a distinction is satisfactory only when the patient has been observed during an attack and later during a period of normal rhythm. Furthermore, a comparison of 200 cases of paroxysmal auricular fibrillation, reported by Parkinson and Campbell[30] with a similar group exhibiting established auricular fibrillation[4] indicates that the different forms of cardiac disease occur in essentially the same percentages in each group. In the paroxysmal fibrillation as opposed to the permanent form, hypertensive heart disease displaces rheumatic heart disease as the commonest cause. Although "infective" or "toxic" causes may be arbitrarily placed in a separate group, in a consideration of the etiology of paroxysmal auricular fibrillation, it is well recognized that there is coexistent organic heart disease in most instances. It is safe to assume that auricular fibrillation, of either the transient or established form, seldom occurs in a perfectly normal heart.

Certainly paroxysmal auricular fibrillation frequently passes over into the established irregularity later and in many of these instances is ultimately shown to have an organic substratum. Parkinson and Campbell[30] have discussed this point in their scholarly review. The occasional exception to this rule must be recognized, however, and there appear to be a number of well-authenticated instances of paroxysmal auricular fibrillation occurring in the complete absence of any evidence of cardiac disease.

Paroxysms of auricular fibrillation, in the absence of evident heart disease, have been shown to result from many causes—drugs, infections, trauma, physical overexertion and numerous other factors. The literature on this subject is fully covered in the articles of Cowan[10] and of Parkinson and Campbell.[30] Digitalis, the most important of the agencies referred to above, will be considered later.

**Auricular Fibrillation in Syphilitic Cardiovascular Disease.** The extreme rarity of auricular fibrillation in cardiac disease due to syphilis has been noted by a number of writers but is not a matter of common knowledge.* Carter and Baker[6] have stressed the point in a recent paper. Auricular fibrillation is so unusual in such

* Fibrillation of the auricles is rare also during the active stages of infective endocarditis,[35] in association with angina[9] and in heart failure due to obstruction in the pulmonary circulation.[25] The low incidence of auricular fibrillation following coronary occlusion has been noted by Parkinson and Bedford.[29] Levine[17] has shown that the percentage is in fact considerably higher. The high incidence (25 per cent of cases of coronary occlusion) observed in the latter series however has little bearing on the subject of permanent auricular fibrillation since in many instances the arrhythmia was temporary and was recognized only by continuous observation in the hospital.

instances that its presence militates strongly against the diagnosis of cardiovascular syphilis in a given case. The reason for this infrequent association is not apparent, unless it be dependent upon the fact that the damage in cardiovascular syphilis is limited to involvement of the aorta and aortic valve, the mitral valve and the myocardium usually being unaffected. Auricular fibrillation is also uncommon in disease of the aortic valve due to causes other than syphilis. Indeed it is less commonly met with in combined lesions of the aortic and mitral valves than in disease of the mitral valve alone. This vexed question of the ultimate cause of auricular fibrillation, although outside of the scope of the present report, will be discussed in brief, later.

In a series of 100 patients exhibiting heart failure with a *normal rhythm*[31] cardiovascular syphilis was present in 21 per cent. On the other hand among Campbell's[4] cases of auricular fibrillation only 2 per cent were associated with syphilitic cardiovascular disease. Similarly but 13 (2.6 per cent) of 499 instances of auricular fibrillation reported by Willius[40] were grouped under aortic insufficiency. No note was made of the etiology of the latter though syphilis was doubtless responsible in the majority of instances. Cowan and Ritchie,[11] over a period of 10 years, saw only 12 cases in which auricular fibrillation was associated with "aortic incompetence."

A positive blood Wassermann reaction was present in 8.6 per cent of Levine's[16] series of 128 cases of auricular fibrillation. This rather high figure fails, however, to indicate the actual incidence of cardiovascular syphilis in his series, since aortic aneurysm was present in 2 instances, aortitis in 2 and "chronic myocarditis or chronic endocarditis and mitral stenosis or both" in 7 instances. Cohn,[7] in quoting the older series of Frey (100 cases) and Semerau (111 cases), has noted that no cases of auricular fibrillation due to syphilitic cardiovascular disease occurred in the former group. Syphilis appeared to be the cause of the arrhythmia in 6.3 per cent of Semerau's cases. It should be noted, however, that 82 of the 111 cases in his series were drawn from military life.

In the present series auricular fibrillation was associated with syphilitic cardiovascular disease in only 3 per cent of the total number of cases. This is especially noteworthy for, due to the large number of negroes seen in this clinic, syphilitic aortitis is recognized as being present in 15.14 per cent of all patients admitted to the hospital with heart disease. The actual occurrence as proven at autopsy is even greater. A review of the records of those patients with cardiovascular syphilis who have exhibited a totally irregular rhythm has brought to light certain instructive facts.

There were 18 cases in this group or a little over 3 per cent of the entire series. At autopsy 1 of these patients had old rheumatic endocarditis with mitral stenosis, syphilitic aortitis with insufficiency of the aortic valves and a huge aneurysm of the aortic arch.

Autopsy in another case demonstrated that there was, in addition to syphilitic aortitis, an extensive arteriosclerosis of the pulmonary artery, probably syphilitic in origin. There was great hypertrophy and dilatation of the right ventricle. Two other patients were young women who at autopsy were shown to have syphilitic aortitis which did not involve the aortic valves. There was extensive myocardial scarring which would seem to be justifiably termed syphilitic myocarditis.* The coronary vessels were normal.

**Induction of Auricular Fibrillation by Digitalis, Especially as Regards Syphilis.** The remaining 14 syphilitic patients presented the classical picture of syphilitic aortitis with aortic insufficiency. Five of these had auricular fibrillation on admission which did not seem to be associated with any form of therapy. In the remaining 9 patients it appears probable that auricular fibrillation was associated with the administration of digitalis. Mackenzie[21] pointed out, in 1911, that auricular fibrillation might result from effective doses of digitalis.† In an earlier report[23] such a case was described although the relationship was not clearly recognized. The single cases reported by Danielopolu,[13] by Nadel[27] and by Neuhof,[28] the 3 cases of Parkinson and Campbell[30] and the 2 of Schwartz[37] appear to be valid instances of this relationship. In 2 earlier cases reported by Schwartz[36] it seems likely that the attacks were precipitated by digitalis. The latter cases are of interest in that auricular fibrillation did not disappear until 4 to 6 weeks respectively after the drug had been discontinued. Some of the instances of auricular fibrillation in Schwartz and Weiss's[38] series of 10 cases in children were, as Cookson pointed out, almost certainly the result of digitalis administration.

In this group with cardiovascular syphilis, fibrillation of the auricles appears to have been induced by digitalis in 9 instances, 5 of which have already been reported by Resnik.[32] In these 5 cases the strict criteria, suggested by Resnik as a basis for judgment upon the relationship between auricular fibrillation and digitalis therapy, were satisfied in every instance, to wit: (1) Absence of history of previous attacks of auricular fibrillation; (2) normal rhythm before administration of digitalis; (3) appearance of auricular fibrillation after a dose of digitalis shown, by clinical and electrocardiographic evidence, to be an effective amount; (4) persistence of the abnormal rhythm as long as digitalis is continued in doses sufficiently large to compensate for the elimination of the drug; (5) reëstablishment of normal rhythm after discontinuance of the digitalis; (6) confirmation of the changes in rhythm by means of electrocardiographic records; (7) exclusion of other factors which tend to bring on transient auricular fibrillation.

Although such criteria are necessary to establish actual proof,

* The cases will be reported in full at a later date.

† Cushny[12] has produced the same phenomenon experimentally in animals.

there are frequent instances in which a patent relationship exists between digitalis therapy and the onset of auricular fibrillation, in which not all of these criteria can be satisfied. This is true of the remaining 4 cases in the group referred to above. These patients all had severe cardiac decompensation, and their electrocardiograms on admission showed normal sinus rhythm. After the administration of digitalis in large doses, clinical signs of the therapeutic effect of the drug were noted, auricular fibrillation ensued and the *T* waves of the electrocardiograms revealed changes that were attributed to the digitalis therapy. After the drug was discontinued, however, the cardiac rhythm in these 4 patients failed to return to normal during the period of our observation, (24, 17, 4 and 2 days respectively after the onset of auricular fibrillation).

It must be pointed out that although the 9 cases reported above fall into the group with cardiovascular syphilis, these cases are discussed merely to emphasize the rarity of auricular fibrillation in this form of heart disease and to illustrate the occasional occurrence of auricular fibrillation following excessive digitalis administration. It is not suggested that there is greater likelihood of digitalis giving rise to fibrillation in syphilitic cardiovascular disease than in other forms of heart disease with normal rhythm. Nor can such a conclusion be drawn from Resnik's series (5 out of 7 had cardiovascular syphilis) since his material was selected. Certainly digitalis was responsible for some of the instances in Schwartz and Weiss's series of auricular fibrillation in children with rheumatic heart disease. We have observed several instances of auricular fibrillation in patients with hypertensive heart disease in which the relationship to digitalis therapy satisfied all of Resnik's criteria. No study seems to be available bearing upon the relative liability to the induction of auricular fibrillation by digitalis in various types of heart disease with normal rhythm. It is possible that a careful analysis of records in all forms of heart disease would reveal more cases in which digitalis was responsible for the onset of auricular fibrillation.

The instances reported to date have been observed in patients exhibiting advanced heart failure and it would seem probable that a greater liability to fibrillation from digitalis exists under these circumstances. It must be remembered, however, that digitalis is usually administered in relatively large doses to such patients. Brams and Gaberman[3] have recently completed a study in which digitalis was administered in large doses* to 9 patients without cardiac disease. Transient auricular fibrillation occurred in 1. We have observed the occurrence of fibrillation as a result of massive doses of digitalis in 1 patient with hypertensive heart disease who

* The usual amounts given were 45 cc. intravenously of potent digifolin over 9 days.

had but mild congestive heart failure. It would appear that in most instances, large doses of digitalis are required to produce the arrhythmia although it is possible that the customary doses may do so in susceptible individuals. Furthermore, although the instances of this relationship reported to date have developed in patients with congestive heart failure, the case noted above and that of Brams and Gaberman[3] show that the phenomenon may occur in the absence of severe congestive heart failure.

It is of interest to note that in auricular fibrillation, induced by digitalis, the ventricular rate is relatively slow. This is due to a coincidental "blocking" action of the drug through the vagus upon the bundle of His, as a result of which a smaller number of the irregular auricular impulses are able to reach the ventricle. Atropin, therefore, by releasing the vagus frequently causes a considerable rise in ventricular rate in such cases despite the fact that by its action on the auricular muscle it actually tends to slow the rate of circus movement to some extent. In 1 of the 7 patients to whom Resnik[32] administered atropin, normal sinus rhythm was reëstablished 68 minutes later apparently as a result of the atropin. A similar but less convincing case has been reported by Hering.[15] The part played by the atropin is doubtful in both instances.

The onset of auricular fibrillation due to digitalis has been preceded in every instance by other evidences of digitalis intoxication, most frequently by the appearance of extrasystoles and coupled rhythm or more rarely by the development of nausea, vomiting, diarrhea and other concomitants of digitalis action. No instance has been noted in which the development of fibrillation seemed to have had any appreciable influence—either for better or for worse—upon the general clinical condition of the patient. After discontinuance of digitalis therapy normal sinus rhythm was usually reëstablished within a few days. It is probable however, that harm would have resulted had the drug been continued and pushed still farther after the onset of fibrillation. Under such circumstances, ignorance of this point would tempt one to push digitalis in the hope of bringing about a normal rhythm whereas discontinuance of the drug would actually offer the best chance of obtaining this result. The latter is therefore not one of academic interest alone.

**The Cause of Auricular Fibrillation.** It is obvious that no one condition and no single set of circumstances can explain the development of auricular fibrillation in all cases. It appears to be a physiologic abnormality occurring most frequently in hearts that are damaged by disease. It has been observed, however, in individuals presenting no evidence whatever of cardiac damage and in such instances is usually of brief duration. In the latter cases there has been, without exception, some factor of infection, toxemia or overexertion that might conceivably have interfered with the normal metabolic processes of the heart. Excellent studies are available relating to the physiology of auricular fibrillation, to the morbid

anatomy of hearts from patients dying with the arrhythmia and to the clinical aspects of the subject. No comprehensive effort has been made however to link these phases together. Such a study would be well worth while.

Why does auricular fibrillation rarely occur in patients who die of syphilitic cardiovascular disease, while it is almost always present before death in the victims of rheumatic endocarditis? Why is the incidence of the arrhythmia lower in patients with combined involvement of the aortic and mitral valves due to rheumatism than in the instances of mitral disease alone? What is responsible for the frequent occurrence of auricular fibrillation in hyperthyroidism—a condition in which no significant organic lesion of the heart is demonstrable?[26] Why is fibrillation uncommon during the acute stages of rheumatic infection when one might suppose that involvement of the myocardium was at its height? These and many other questions remain unanswered. Brief reference to these problems has been made in the papers of Yater,[41] of Robinson[34] and of Gossage and Hicks.[14]

In a consideration of the ultimate cause of auricular fibrillation, 3 obvious possibilities suggest themselves. First, that the normal processes of conduction within the auricles are disrupted as a result of morbid structural changes in the muscle fibers. That such a factor is of great importance is evidenced by the fact that the arrhythmia occurs in the vast majority of instances in individuals with organic heart disease. Many reports are now available, however, bearing upon the morbid anatomy of hearts from individuals who have exhibited auricular fibrillation during life. There is general agreement that no lesion can be found that is specific for or distinctive of the arrhythmia. Changes, when found, differ in no way from those observed frequently in the hearts of individuals who had normal rhythm during life. Conversely, in a number of instances of auricular fibrillation no pathologic changes whatever have been demonstrable in the hearts at autopsy. Yater[41] has recently reviewed the literature and has published a large number of personal observations. The reader is referred to his paper for a full discussion of the subject.

In the second place the frequent occurrence of aurcular fibrillation in hearts that are the seat of organic disease is susceptible of another explanation than the mere disruption of normal pathways of conduction in the auricles by structural areas of block. The nutrition and the metabolic processes of the auricular muscle in such circumstances must be profoundly altered. The occurrence of auricular fibrillation in apparently normal hearts following overexertion, hydrogen sulphid poisoning, induced hyperthyroidism, the anoxemia of pneumonia, alcoholic excesses, digitalis therapy and numerous other drugs and causes is evidence of the profound influence that may be produced by alterations in the metabolic activities of the heart. The long continued overwork and high auricular pressures

incident to mitral stenosis may produce changes in the nutrition of the auricular muscle of somewhat similar character.

Considerable experimental evidence lends weight to such a conception. Thus auricular fibrillation can be induced in animals, with ease by asphyxia. Similarly large doses of digitalis by direct action on the auricular muscle may bring on the arrhythmia even in perfused hearts. The stimulating paper of Carter, Andrus and Dieuaide[5] is illustrative of the fundamental changes that may occur in the development and propagation of the excitatory impulse in the heart as a result of anoxemia, alterations in the pH of the circulating fluid and similar factors. Such influences are even yet imperfectly understood when applied experimentally. It is entirely impossible at the present time to assess their significance in the production of auricular fibrillation in the human being.

The third factor—that relating to nervous influences is still largely of academic interest. Lewis, Drury and Bulger[19] have called attention to the occasional occurrence of auricular fibrillation during vagal stimulation in experimental animals. Andrus and Carter[1] have shown that during vagal stimulation a single induction shock, introduced soon after the end of the refractory period, frequently produces auricular fibrillation. It is conceivable that in some instances conditions of increased vagal tone may play a part in the production of auricular fibrillation in the human.

It is impossible to state the relative importance of these three factors in the genesis of clinical auricular fibrillation. Any one or all three elements may be responsible in a given case. The final answer would appear to lie in further studies of the interrelationship between the cardiac arrhythmias and certain fundamental changes in the metabolism of the myocardium.

**Summary.** 1. A study has been made of 575 consecutive cases of auricular fibrillation confirmed by electrocardiographic records.

2. The etiologic relationships to the various forms of cardiac disease are tabulated.

3. The infrequent occurrence of the arrhythmia in the first decade of life is discussed and 2 additional instances are recorded.

4. Emphasis is laid upon the rarity of auricular fibrillation in syphilitic cardiovascular disease. In the present series, 35 per cent of cases were associated with rheumatic heart disease and only 3 per cent with syphilitic cardiovascular disease.

5. Note is made of the production of auricular fibrillation by administration of digitalis.

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# THE ETIOLOGY, PROGNOSIS AND TREATMENT OF AURICULAR FIBRILLATION.* †

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The subject of auricular fibrillation has occupied the attention of many notable workers, especially since 1909 when its relatively common incidence was first noted by Rotherberg and Winterberg[1] and by Lewis.[2] The inconsistency of its appearance in the various forms of cardiovascular disease, in fact even in the absence of any demonstrable cardiovascular damage, and the variable duration of life following its onset, have caused a general uncertainty as to its etiology, prognosis and treatment. The widespread impression that its occurrence foreshadows imminent death is in marked contrast to the number of patients in whom the duration of life after the onset of auricular fibrillation has been from 5 to 15 years. Is the answer to this inconsistency to be found in the etiology, age of onset or in the treatment of these cases? The published works of Paul White,[3] Willius,[4] Cohn[5] and Jones[6] have proved most interesting and have prompted us to examine our own series in the hope of throwing some further light on this subject.

The present series consists of some 253 cases treated in our

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private practice or in the wards or heart clinic of the Pennsylvania Hospital in Philadelphia. Only chronic fibrillators have been included, those having paroxysmal fibrillation or in whom normal sinus rhythm returned spontaneously have been eliminated. These cases have been followed over a period of at least 1 to 18 years after the onset of fibrillation. The diagnosis has been confirmed by electrocardiograms in each case. We have endeavored to discover first: Some universal cause; none has thus far become apparent. Second: Some standards by which to estimate the probable duration of life in cases of chronic auricular fibrillation. We have some definite impressions in this direction. Third: The most satisfactory method of treatment. In this we believe our observations are of definite value.

**Etiology.** In respect to etiology, we have divided our cases into those which were obviously of rheumatic origin and those of the "nonrheumatic" or so-called arteriosclerotic type. We have included in the rheumatic group those with a definite mitral stenosis even in the absence of a history of a typical arthritis accompanying rheumatic fever, chorea and "growing pains." We have not divided our so-called arteriosclerotic or "nonrheumatic" group into those with and without hypertension, although we realize the desirability of so doing. A third or miscellaneous group includes cases of thyrotoxic etiology, others presumably luetic, since they had manifestations of cardiovascular syphilis and, finally, those cases in which no etiologic factor was apparent. These three categories are comparatively well defined, although occasionally it is difficult to distinguish between cases of the arteriosclerotic and miscellaneous types. In them, however, we have been able to determine no factor which they share in common, either clinical or physiologic, which might account for the incidence of fibrillation. These cases differ in every apparent respect, including etiology, family history, occupation, age of infection, age of onset of fibrillation and degree of cardiac disability at the time of onset of the arrhythmia. There is apparently nothing to distinguish beforehand those cardiacs who will fibrillate from those who will not.

It will be seen here from Table 1 that of the 781 cases of cardiovascular disease admitted to the wards of the Pennsylvania Hospital during a period of 3 years auricular fibrillation occurred in 48 (25 per cent) of the 197 rheumatics, 52 (21 per cent) of the 247 sclerotics, and 38 (19 per cent) of the 199 with miscellaneous etiology. One may anticipate, therefore, that of the rheumatics, 1 out of every 4 patients will develop auricular fibrillation and of the others 1 out of every 5.

As to pathology, it has been well demonstrated by Yater[7] from a comparative examination of 29 hearts which had previously fibrillated with a series of clinically similar cases which had not, that there is no characteristic pathologic difference. In fact, in

the arteriosclerotic group a greater degree of vascular sclerosis was frequently found in cases where fibrillation did not occur, while the fibrillators themselves often manifested practically no abnormal vascular changes. Our own findings lead us to agree with White,[8] who states that "There is no pathology characteristic of auricular fibrillation."

TABLE 1.—INCIDENCE OF HEART DISEASE IN WARDS OF THE PENNSYLVANIA HOSPITAL OF PHILADELPHIA, FOR A 3-YEAR PERIOD.

| | 1928. | 1929. | 1930. | Totals. |
|---|---|---|---|---|
| With auricular fibrillation: | | | | |
| Arteriosclerotic | 16 | 15 | 21 | 52 |
| Rheumatic fever | 18 | 19 | 11 | 48 |
| Syphilitic | 4 | 2 | 1 | 7 |
| Thyroid | 2 | 3 | 1 | 6 |
| Unknown | 6 | 10 | 9 | 25 |
| Total | 46 | 49 | 43 | |
| Without auricular fibrillation: | | | | |
| Arteriosclerotic | 78 | 67 | 102 | 247 |
| Rheumatic fever | 72 | 68 | 57 | 197 |
| Syphilitic | 42 | 35 | 38 | 115 |
| Thyroid | 0 | 1 | 1 | 2 |
| Unknown | 28 | 31 | 23 | 82 |
| Total | 220 | 202 | 221 | |
| Total with and without auricular fibrillation | 266 | 251 | 264 | 781 |

TABLE 2.—ETIOLOGY OF AURICULAR FIBRILLATION.

| | No. of cases. | Rheumatics, per cent. | Total, per cent. |
|---|---|---|---|
| Rheumatic: | | | |
| Arthritis | 73 | 59 | |
| Chorea | 3 | 2 | |
| Arthritis and chorea | 5 | 4 | |
| Tonsillitis | 17 | 15 | |
| No history | 24 | 20 | |
| Total rheumatic fever | 122 | .. | 48.0 |
| Arteriosclerosis | 88 | .. | 35.0 |
| Syphilis | 23 | .. | 9.0 |
| Thyroid | 9 | .. | 3.5 |
| Miscellaneous | 11 | .. | 4.5 |
| Total | 253 | | |

It will be seen from Table 2 that of our 253 cases 122 (48 per cent) were associated with rheumatic fever. Of these over one-half were of the arthritic type. The others, including chorea, tonsillitis and those which, due to the presence of mitral stenosis, we believe are of rheumatic etiology in spite of the absence of a definite rheumatic history. The arteriosclerotic group includes 88 (35 per cent). We agree with Cookson[9] that the title of this group should probably be "nonrheumatic" rather than arteriosclerotic. Of the miscellaneous group, comprising 43 cases (17 per cent) of

the total, over one-half were associated with positive blood Wassermanns and definite clinical evidence of cardiovascular syphilis. The relationship of syphilis to auricular fibrillation is, at best, uncertain. Stokes[10] states: "My impression has been that the more cardiovascular syphilis I have seen, the less auricular fibrillation; and the more auricular fibrillation, the less cardiovascular syphilis." In the recent reports from the Johns Hopkins Hospital[11] there was an entire absence of auricular fibrillation in a series of 100 cases of syphilitic cardiac disease. The small number of fibrillators with thyrotoxicosis, on the other hand, is not due to the infrequent complication of auricular fibrillation with goiter, but rather to the extremely low incidence of thyroid disease in the heart clinic and on the wards of the Pennsylvania Hospital.

It would appear, therefore, that while auricular fibrillation tends to occur consistently in a definite percentage of certain types of heart disease, its exciting cause is totally unknown. That the mechanism is one of abnormal conduction in the auricular muscle, as suggested by Garrey[12] and Mines,[13] and recently supported by Lewis,[14] seems at present the most plausible explanation. However, in the absence of detectable pathology such abnormal conduction in turn implies the presence of some factor affecting auricular metabolism which should be common to all cases, and the nature of which is as yet only vaguely conceived. That such a factor is not necessarily permanent is obvious from the existence of the paroxysmal types of fibrillation. That it must be persistently acting, and has not merely to initiate the arrhythmia, is apparent to all who are familiar with the extreme difficulty of producing persistent fibrillation of the normal auricle in experimental animals.

TABLE 3.—SEX INCIDENCE IN AURICULAR FIBRILLATION.

| | No. of cases. | | Per cent. | |
|---|---|---|---|---|
| Etiology. | Males. | Females. | Males. | Females. |
| Rheumatic fever | 72 | 50 | 59 | 41 |
| Arteriosclerosis | 57 | 30 | 65 | 35 |
| Syphilis | 22 | 1 | 96 | 4 |
| Thyroid | 3 | 6 | 33 | 67 |
| Miscellaneous | 10 | 2 | 83 | 17 |
| Total | 164 | 89 | 65 | 35 |

SEX. The sex incidence is of interest. It will be seen in Table 3 that our series includes 164 males (65 per cent) and 89 females (35 per cent), a preponderance of 30 per cent in favor of the males. These figures are almost identical with those of Semerau[15] and not greatly at variance with those of Lewis.[16] Cookson,[17] however, has reported a ratio of at least 2 to 1 in favor of women. We are inclined to believe that auricular fibrillation really predominates significantly in the male, although the figures are undoubtedly modified by the preponderance of cardiovascular disease among

men. This greater incidence is possibly explainable on the basis that with the onset of cardiovascular disease there is a greater tendency for men to continue with their work to the extent of overexertion than for women, who, in general, have more leisure for therapeutic rest.

**Prognosis.** Some of the most helpful facts to be learned from a statistical study of cardiovascular cases are those bearing on prognosis. Granted that to date our therapeutic measures can achieve only a limited prolongation of life in most types of cardiovascular

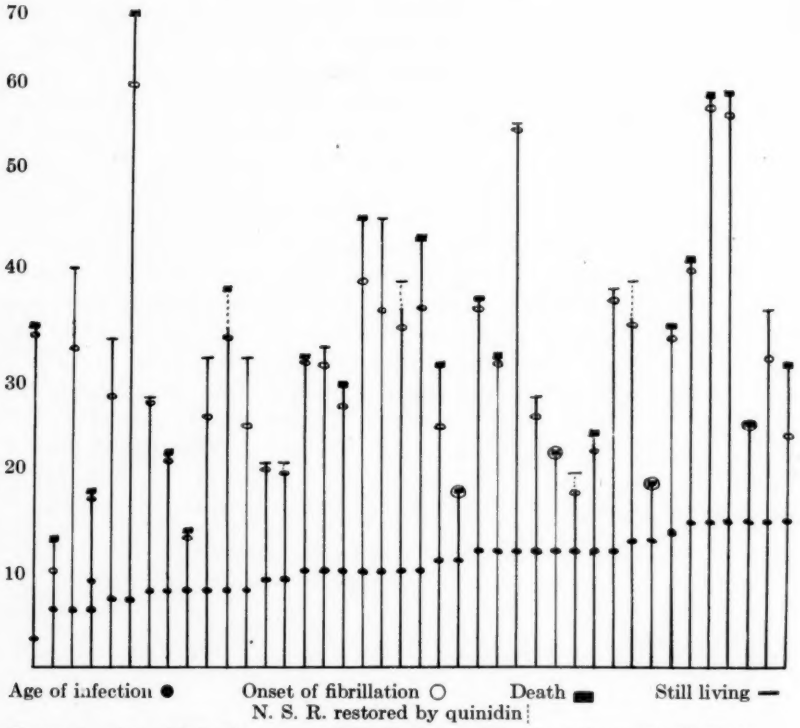


CHART I.—Age of infection; onset of fibrillation and death of rheumatic fibrillators.

disease, it becomes increasingly important that we be able to advise the patient as to the probable duration of his active life and the onset of his years of total disability, in order that he be able to arrange his economic and domestic affairs accordingly.

Charts I and II indicate the ages of infection, fibrillation and death of our rheumatic patients. Of the 77 cases illustrated 51 (66 per cent) developed their etiologic infection before the age of 20 years; 37 (73 per cent) of their number began to fibrillate between the ages of 20 and 40 years, and in this group the average duration of life was about 3 years thereafter; 7 (13 per cent) began to fibrillate

before 20 years, and their subsequent duration of life was less than 1 year. The remaining 7 (13 per cent) whose arrhythmia started after 40 years of age fibrillated for an average of 5 years.

It becomes apparent then that the age of onset of the fibrillation is of considerable importance in determining the life expectancy of the patient. Other things being equal, those hearts which are least damaged by a rheumatic infection should probably begin to

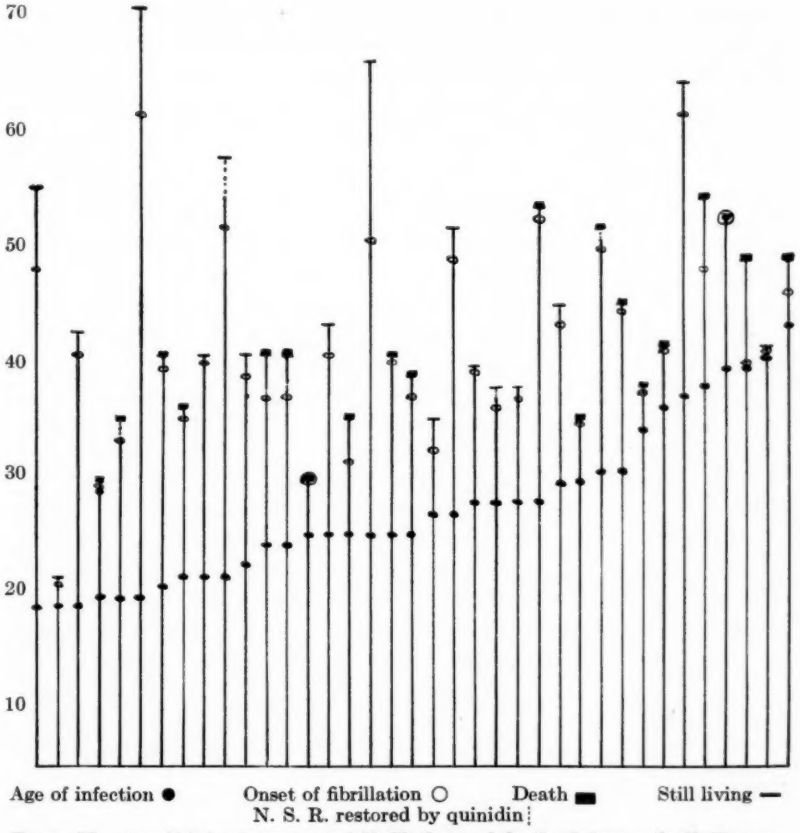


CHART II.—Age of infection; onset of fibrillation and death of rheumatic fibrillators.

fibrillate later and last longer thereafter than those in which the etiologic infection has been more destructive. Among the 26 (33 per cent) of the total group whose infection occurred after 20 years the average duration of life was about the same as the general average, that is, 2½ to 3 years.

As to the comparative severity of the various forms of rheumatic infection, an indication will be found in Tables 4 and 5. A combination of arthritis and chorea is associated with the earliest

appearance of fibrillation and with a life expectancy of less than 1 year following its onset. Severe streptococcic tonsillitis is almost as ill-omened, while simple arthritis appears to give the best prognosis, with a duration of life of 2 to 3½ years after fibrillation and a maximum length of fibrillation in our experience of 16 years. Generally speaking, if we are justified in placing importance upon our results, of those patients with a history of rheumatic fever with resultant rheumatic cardiovascular damage before the age of 25 years, and who are going to develop auricular fibrillation, 86 per cent will develop this arrhythmia before the age of 40 years and 88 per cent will have died before the age of 53 years.

TABLE 4.—ETIOLOGY AND PROGRESS OF FIBRILLATORS NOW LIVING

| Etiology. | No. of cases. | Age at etiological history. | Age at onset of cardiac symptoms. | Age at onset of fibrillation. | Age at onset of congestive failure. | Duration of fibrillation, years. | Maximum life after onset of fibrillation, years. |
|---|---|---|---|---|---|---|---|
| Rheumatic: | | | | | | | |
| Arthritis | 32 | 18 | 34 | 41 | 37 | 3½ | 16 |
| Chorea | 1 | 8 | 28 | 28 | 28 | 2 | 2 |
| Chorea and arthritis | 2 | 11, 10 | 26 | 29 | .. | 2 | 2 |
| Tonsillitis | 10 | .. | 31 | 35 | 27 | 3 | 8 |
| No history | 12 | .. | 34 | 38 | 39 | 2 | 3½ |
| Arteriosclerosis | 47 | .. | 58 | 60 | 62 | 2½ | 8 |
| Syphilis | 9 | 36 | 53 | 55 | 61 | 2 | 3 |
| Thyroid | 5 | 39 | 40 | 42 | 51 | 2 | 3 |
| Unknown | 12 | .. | 41 | 45 | 40 | 3½ | 11 |

TABLE 5.—ETIOLOGY, PROGRESS AND TERMINATION OF DECEASED FIBRILLATORS.

| Etiology. | No. of cases. | Age at etiological history. | Age at onset of cardiac symptoms. | Age at onset of fibrillation. | Age at onset of congestive failure. | Age at death. | Duration of fibrillation, years. | Maximum life after onset of fibrillation, years. |
|---|---|---|---|---|---|---|---|---|
| Rheumatic: | | | | | | | | |
| Arthritis | 41 | 18 | 30 | 36 | 36 | 38 | 2 | 6 |
| Chorea | 2 | 8 | 30 | 35 | 36 | 38 | 2 | 4 |
| Chorea and arthritis | 3 | 11–18 | 21 | 27 | 27 | 28 | 1 | 1 |
| Tonsillitis | 7 | .. | 29 | 30 | 30 | 31 | 1½ | 5 |
| No history | 13 | .. | 34 | 38 | 40 | 41 | 3 | 6 |
| Arteriosclerosis | 42 | .. | 57 | 58 | 60 | 63 | 3 | 11 |
| Syphilis | 14 | 30 | 50 | 52 | 52 | 54 | 2 | 7 |
| Thyroid | 4 | 24 | 32 | 44 | 45 | 46 | 2 | 3 |
| Unknown | 6 | .. | 45 | 49 | 46 | 51 | 2 | 4 |

The arteriosclerotic type presents a rather different picture. Here the onset of fibrillation is frequently the first manifestation of heart disease, and with few exceptions occurs at a later date than

in the rheumatic group. Of our 88 patients with arteriosclerotic or "nonrheumatic" cardiovascular disease who developed auricular fibrillation none developed this arrhythmia before the age of 40 years and 72 per cent after the age of 53 years.

Much dissention exists as to which category offers the better prognosis of life expectancy, Coffen,[18] Cowan and Ritchie[19] and Jones[20] favoring the rheumatic type, while Clerc and Stieffel[21] and Cookson[22] find a better prognosis in the arteriosclerotics. Our own figures show a negligible difference, both groups averaging 2½ years among those now deceased and 3½ years among those still living. We feel in these two groups the comparative prognosis of life after fibrillation develops bears very little relation to etiology. The prognosis is best when fibrillation starts between 25 and 65 years of age irrespective of etiology, our maximum duration of fibrillation being 16 years in the rheumatic group and 14 years in the sclerotic group. Above and below these ages, however, the life expectancy is very short. Examination of Charts I and II, on the other hand, will point out a fact which must not be lost sight of in accepting the evidence of any statistics, namely, that a very definite group of patients die promptly after the onset of fibrillation and that these are balanced by an equal number who live far past the average life expectancy, irrespective of etiology or age of onset. This error will appear in even the largest series of cases, and for this smaller group the average prognosis must be modified by the judgment of the physician. It must be constantly borne in mind that the auricular fibrillation itself is apparently of very slight importance in determining the functional efficiency or duration of life of the patient compared to the severity of the myocardial damage. And, conversely, the extent of the myocardial damage beyond a certain degree is in no way indicated by the presence or absence of fibrillation. The residual myocardial reserve is the all-important factor.

The third group, those of miscellaneous or unknown etiology, are of comparatively indefinite characteristics. In thyrotoxicosis we have found that the majority of cases return spontaneously to normal sinus rhythm after partial thyroidectomy. The infrequency of fibrillation in cardiovascular lues, on the other hand, marks its onset as a bad prognostic omen. One of our cases has lived 7 years, but the average duration of life after fibrillation is only 2 years, which is the shortest of these groups. Finally, 11 cases (4.5 per cent) of our total series have had no apparent etiologic nor clinically demonstrable cause for their auricular fibrillation. Their average duration of life was 2 to 3½ years. The average age of onset of fibrillation was 46 years as compared with 38 years for the rheumatics and 59 for the sclerotics.

Chart III presents graphically the duration of fibrillation in all our cases, irrespective of etiology, and will be referred to later

*apropos* of quinidin therapy. It indicates well, however, the number of patients who die promptly after the onset of fibrillation.

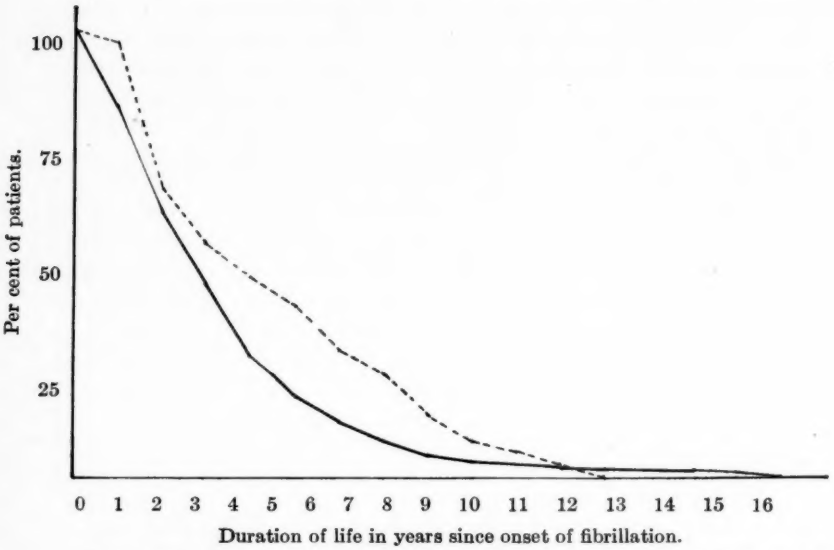


CHART III.—Comparative duration of life after onset of auricular fibrillation in cases successfully treated with quinidin and cases either unsuccessfully treated or untreated with quinidin.

———— Patients without quinidin or unsuccessfully treated with quinidin (219 cases).

– – – – – Patients who had a return of N. S. R. with quinidin (40 cases).

**Treatment.** The treatment of auricular fibrillation comprises an added factor not present in the case of a diseased cardiovascular system, but with a nonfibrillating heart. Primarily, one seeks, as with the average cardiac, to restore to as great a degree as possible the reserve of the myocardium. Secondarily, however, the physiologic deficiency of the arrhythmia must be overcome. This latter may be accomplished either by restoring the normal sinus rhythm or by eliminating the pulse deficit. The therapeutic procedures involved in effecting the former by means of quinidin sulphate and the latter by digitalization need not be discussed here. Both are now standardized routine in all clinics and our own methods have been described by us in a previous paper.[23]

As to the results with quinidin, Wolff and White[24] have reported the successful restoration of sinus rhythm in 65 per cent of their series of 177 cases. This is about the average optimum. In our own series of 66 cases quinidin was effective in restoring the normal sinus rhythm in 40 patients (66 per cent). In a previous paper we reported our enthusiasm at these results. Since then, however, having followed these cases in the *interim*, amounting in some to

a period of over 7 years, our views have become less sanguine. These are mostly well-selected cases with the most favorable prognoses and with a minimum of determinable myocardial damage. Practically none of these cases developed congestive circulatory failure to any marked degree, in spite of the onset of auricular fibrillation. Nevertheless their average duration of life following the onset of auricular fibrillation was only slightly over a year longer than that of the patients who were considered unsatisfactory for quinidin therapy and exactly the same as that of the patients who had received quinidin but without the restoration of normal sinus rhythm. Surprising as these observations may be, they are quite in accord with the conclusions of Wolff and White,[25] that "there is no definite evidence that it (quinidin) prolongs life or reduces mortality."

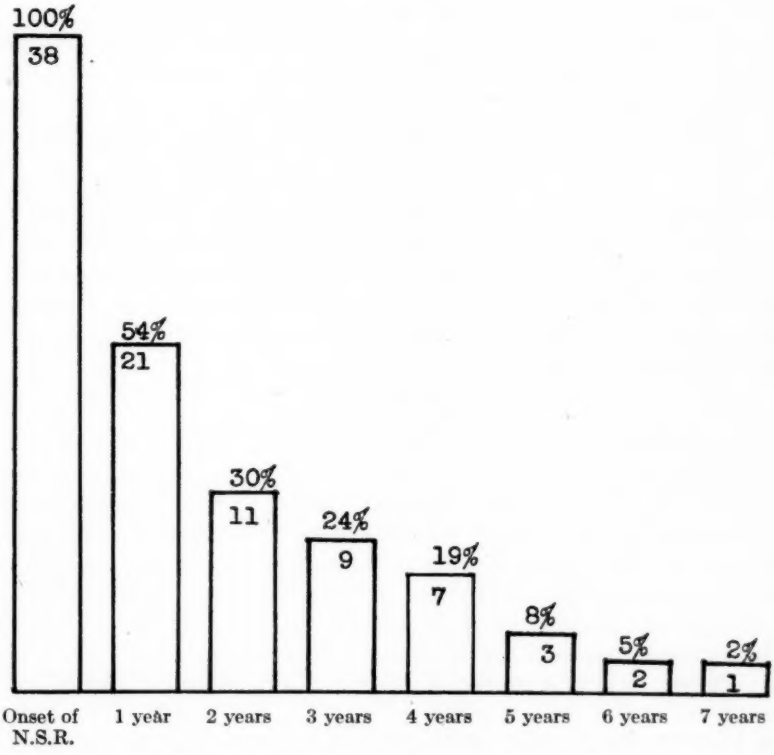


CHART IV.—Duration of normal sinus rhythm restored in 38 of 62 cases of chronic auricular fibrillation to whom quinidin sulphate was administered.

The average duration of sinus rhythm in our successful quinidin patients was 1½ years, as indicated by Chart IV. In about one-half of the series it lasted less than 1 year; 1 out of every 4 lasted through

2 years; 1 out of 5 lasted through 3 years; 1 out of 20 lasted through 5 years. One case of the entire series preserved his normal sinus rhythm for 7 years and has just had a return to fibrillation. Marvin and White,[26] however, report somewhat better results, in that 30 per cent of their cases have continued with normal sinus rhythm for 6 to 7 years.

Obviously it is only in the cases where normal sinus rhythm is restored for a substantial length of time that quinidin may be said to be of definite value. On the other hand, we have found that the majority of our patients with restored sinus rhythm were no less "heart conscious" than during the period of their fibrillation under effective digitalis therapy. They were usually in a state of apprehension of the moment when fibrillation would return and thus necessitating the comparatively severe therapeutic régime of a second attempt to restore sinus rhythm.

In terms of the physiology of the circulation it is really very questionable whether the arrhythmia causes nearly as much circulatory embarrassment as one might *a priori* anticipate. Lewis[27] has shown that with the onset of fibrillation produced experimentally in laboratory animals there is an immediate fall in blood pressure, followed, after a brief interval, by a return to within the normal range. Clinically, such is unquestionably the case when the rate of the fibrillating heart is normal and there is no pulse deficit. Such a status is achieved in most cases by digitalis therapy. We feel, therefore that quinidin is indicated only in a comparatively few carefully selected cases of younger individuals in whom there is apparently no other evidence of cardiovascular abnormality except the auricular fibrillation.

As to the incidence of sudden death following the use of quinidin, only 2 cases of such an accident occurred in our series. In neither of these instances do we feel that quinidin could be fairly indicted as similar occurrences of equal frequency have been reported among cases to whom no quinidin had been given and who had comparable cardiovascular pathology. Our feeling in this regard is in concurrence with Viko, Marvin and White,[28] Parkinson and Campbell[29] and Lewis,[30] who believe that the incidence of embolism and sudden death among patients carefully treated with quinidin is no greater than in a control digitalis group.

**Summary.** In a series of 253 cases of chronic auricular fibrillation we have endeavored to determine: (1) The principal etiologic factors; (2) the prognosis on a basis of etiology, age and extent of cardiac damage; (3) the comparative merits of treatment with digitalis and quinidin.

Throughout the series no common etiologic factors have become apparent. It is our impression that the presence of auricular fibrillation does not necessarily imply a worse prognosis than in the non-fibrillating heart with an equal amount of cardiovascular damage.

In our series the average age of onset of auricular fibrillation due to rheumatic cardiovascular damage in 39 years. The prognosis is very poor in such patients developing fibrillation before the age of 25 years. Of our 65 patients with manifestations of rheumatic cardiovascular disease before the age of 25, 86 per cent had developed auricular fibrillation before the age of 40 years and 88 per cent had died before the age of 53 years.

The average age of onset of auricular fibrillation in our arteriosclerotic ("nonrheumatic") group is about 59 years. Of our 88 cases none had begun to fibrillate before the age of 40 years and 72 per cent developed auricular fibrillation after the age of 53 years.

Fibrillation associated with thyrotoxicosis will usually terminate spontaneously following partial thyroidectomy, and if not, almost invariably will respond promptly to quinidin therapy after such an operation.

Syphilitic cardiovascular disease is comparatively rarely associated with auricular fibrillation.

In the treatment of patients with auricular fibrillation digitalis usually proves most satisfactory. It is only in the exceptional case that a restoration to normal sinus rhythm by quinidin sulphate is of more apparent value to the patient than the establishment of a daily maintenance dose of digitalis.

Although there appears to be little danger of accident from the use of quinidin sulphate in properly selected cases of auricular fibrillation, yet we feel this drug should only be used in those few cases of younger individuals with slight or no demonstrable cardiovascular abnormality except the arrhythmia, or in thyrotoxic patients following partial thyroidectomy without a spontaneous return to normal sinus rhythm.

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## SUBACUTE BACTERIAL ENDOCARDITIS, WITH SPECIAL REFERENCE TO THE VALVULAR LESIONS AND PREVIOUS HISTORY.

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There has been much written and taught concerning subacute bacterial endocarditis in recent years and at present the diagnosis in most cases is not difficult. Certainly the younger practitioners and medical students are quite familiar with its commoner manifestations so that the diagnosis is ordinarily suspected in general practice, even though the absolute decision may require laboratory or more expert aid. An aspect of this disease which has not been particularly investigated is the relation between the past history and the previous heart findings to the subsequent development of subacute bacterial endocarditis. It has occurred to us that certain individuals are more liable, and others are less liable to develop this condition. The study here reported has been concerned mostly with this phase of the question, although other clinical considerations have been investigated that seemed to be of interest.

Some reference already has been made to incompatibilities between certain findings in the heart and this disease. For example Libman and associates[1,2] called attention to the great rarity of auricular fibrillation in subacute bacterial endocarditis. Libman[2] also noted the infrequency of this disease in patients "suffering

from marked so-called decompensation." Levine[3] noted that subacute bacterial endocarditis seldom develops in patients with well marked mitral stenosis and believed it was more common in patients who had a well compensated mitral or aortic insufficiency, despite the fact that mitral stenosis is the most common rheumatic valve lesion. At this time no proof was offered for this opinion, but recently Sprague[4] investigated the size of the mitral valve in 20 autopsied cases of subacute bacterial endocarditis, and concluded that well-marked constriction of the mitral valve was uncommon.

Previous reviews of this subject have emphasized the great frequency with which the mitral valve is involved in subacute bacterial endocarditis. Thayer's[5] figures for 60 cases were 80 per cent and 58 per cent for mitral and aortic involvement respectively. Clawson[6] in 72 cases found the mitral valve affected in 76 per cent, the aortic in 47 per cent. Out of 146 cases studied, Blumer[7] found the mitral valve alone involved in 40 per cent, the aortic alone in but 11 per cent. On the other hand, several observers[8, 9, 11] were of the opinion that the aortic valve was more frequently involved. A few years ago when the opinion was expressed in conversations with some American physicians who have been particularly identified with this subject, that subacute bacterial endocarditis was comparatively rarely seen in patients with mitral stenosis, this idea was thought to be untrue. Confusion we believe has resulted because it was inferred from the great frequency of mitral valve involvement in subacute bacterial endocarditis that mitral stenosis was the valvular lesion present in these cases. The data presented here confirm our opinion that although the mitral valve is a common site for subacute bacterial endocarditis, mitral stenosis is rare.

A further feature that has interested us for some years has been the relationship between the previous general health of the patient, the degree of rheumatic infection, and the susceptibility to subacute bacterial endocarditis. It has been very striking that so many of these patients had been comparatively free from recurrent rheumatic infections and had been able for years to carry on their usual activities satisfactorily just preceding the onset of the final illness. Contrariwise, it has also seemed that those patients who were much more sickly and had frequent recurrent bouts of rheumatism did not generally succumb to subacute bacterial endocarditis. An investigation in this regard was made of the cases reported below.

**Material Analyzed in This Study.** All of the cases of subacute bacterial endocarditis observed in the medical wards of the Peter Bent Brigham Hospital from 1913 to 1930 and those seen by one of us in private consultation practice during the past 11 years were analyzed. Only those cases were included in which a review of all of the clinical data made the diagnosis quite certain. There were 111 such cases in 30 of which postmortem examination was performed. There were 67 males and 44 females. The ages varied

from 12 to 64 years. A detailed discussion of the relation of age to this disease will be taken up below. In 95 cases blood cultures were obtained during life, and in 67 of these the cultures were positive. The other 28 showed negative blood cultures, although in 8 instances only one culture was taken during life. In 5 of the negative cases, positive results were obtained on culturing the blood at autopsy. Except for 2 cases that showed atypical organisms, Streptococcus viridans was the organism isolated in all the positive cases.

**The Valvular Lesions in Subacute Bacterial Endocarditis.** It is generally agreed that subacute bacterial endocarditis becomes engrafted on previously injured valves. Although this injury is most frequently the result of an antecedent rheumatic endocarditis, in a much smaller number of cases the defect in the endocardium is congenital in nature. Unlike pneumococcus and gonococcus endocarditis subacute bacterial endocarditis due to Streptococcus viridans rarely if ever develops in a previously undamaged heart. It is difficult to obtain the absolute proof of such a generalization because it would necessitate careful and repeated observation of the heart by the same observer both before and after the development of this disease. At times it is even difficult at autopsy to be certain that a previous valvulitis existed. There is some indirect evidence, however, that lends support to this view. In the first place, it is extremely rare to fail to find some sort of a murmur in cases of subacute bacterial endocarditis. All but 1 of the 111 cases in this review showed at least a systolic murmur. The one exception occurred in a woman who was first seen only 5 days before she died and the heart at this time was very rapid. There is reason to believe that a heart murmur was present at a previous time because a diagnosis of heart disease had been made 2 years before. The constancy of the finding of heart murmurs obtains even during the very early stages of the disease, although murmurs may change in character and new ones develop. Second, in an appreciable number of our cases it was definitely known that a heart murmur was present for many years before the development of subacute bacterial endocarditis. Finally, as a purely clinical experience we have never seen a patient showing no heart murmurs whatever who subsequently developed subacute bacterial endocarditis unless they had an intercurrent infection resulting in a heart murmur between the time of the first examination and the final illness. From the above evidence we are of the opinion that a previous injury to the endocardium, either acquired or congenital, is a prerequisite for the subquent development of subacute bacterial endocarditis due to Streptococcus viridans. As a practical corollary, one can dismiss the diagnosis of subacute bacterial endocarditis in any doubtful case if no murmurs whatsoever are present. If there are exceptions to these general rules, they must be extremely rare.

The type of valvular disease present in the 111 cases in this study was analyzed from a clinical point of view. The 30 autopsied cases were also reviewed and these served as an important control on the interpretation of bedside findings. There were 23 instances in which a systolic murmur alone was heard over the precordium. This murmur was generally best heard at the apex and varied in intensity from moderate to very loud. We interpreted this as indicating mitral endocarditis with mitral insufficiency. The validity of this interpretation is borne out by the fact that in all 4 of the cases of this group in which an autopsy was done, the endocarditis was confined to the mitral valve and there was no mitral stenosis.

There were 66 patients that showed a systolic murmur at the apex and a systolic and aortic type of diastolic murmur at the base of the heart. These were all grouped as having aortic and mitral insufficiency. Twelve of them showed a sufficiently prominent diastolic murmur at the apex to suggest the possibility of mitral stenosis. It is well known that the interpretation of a diastolic murmur at the apex in the presence of aortic insufficiency is difficult, for it may be the same aortic diastolic murmur that is present at the base of the heart which is loud enough to be heard at the apex. Even if it is presystolic in time it may yet be the Austin Flint murmur without mitral stenosis. Not infrequently in this group of aortic cases competent observers incorrectly made a diagnosis of mitral stenosis on the basis of an apical presystolic murmur and thrill. In fact there were 5 instances in which a definite apical presystolic murmur was heard, 4 of which also had a presystolic thrill, that did not show mitral stenosis at postmortem examination. Moreover there were 2 cases in which the Roentgen ray finding of fullness in the region of the left auricle suggested mitral stenosis that was not subsequently confirmed at autopsy. It follows that in patients with subacute bacterial endocarditis who have aortic insufficiency, the additional diagnosis of mitral stenosis must be made with caution, even when there is a presystolic thrill at the apex of the heart.

The second major group of these 66 cases that was analyzed included those with evidence of aortic valvular disease which also showed a mitral systolic murmur. There were 54 of these, all of whom had aortic insufficiency and 10 of them had signs of aortic stenosis as well. We do not imply that such aortic cases with an apical systolic murmur necessarily had a mitral vegetative endocarditis, for many of them may well have had a mitral systolic murmur due to relative insufficiency resulting from the enlargement of the left ventricular cavity, which accompanies aortic disease. This is even true when the apical systolic murmur is loud. In fact of 21 cases that were examined at autopsy, 13 showed vegetative lesions on both aortic and mitral valve and 8 only on the aortic valve, despite the fact that they all showed a mitral systolic murmur.

It may be added that in no case showing aortic and mitral murmurs was the vegetative process confined to the mitral valve. In other words, with clinical signs of aortic involvement there were always vegetative lesions on the aortic valve. Conversely every case that showed vegetations on the aortic valve at autopsy had an aortic diastolic murmur during life.

There are three significant conclusions to be drawn from these observations. First, the presence of a systolic murmur alone indicates a lesion confined to the mitral valve. (One exception to this is the rare instance of aortic stenosis or congenital heart disease with a systolic murmur in which no diastolic murmur is heard.) Second, an aortic diastolic murmur which generally is accompanied by an apical systolic murmur always indicates involvement of the aortic valve with which there may or may not be a lesion of the mitral valve. Finally, in the absence of an aortic diastolic murmur or definite signs of aortic stenosis, it can be predicted that the aortic valves will show no vegetations.

An important consideration in this study is the actual frequency of mitral stenosis in our cases of subacute bacterial endocarditis. (By mitral stenosis is meant a definite constriction of the orifice which during life produces the customary signs and at autopsy shows an appreciable narrowing of the valve.) This can be analyzed from either bedside or postmortem findings. The difficulties of the clinical diagnosis especially in the presence of aortic disease have been discussed above. But even where the disease is confined to the mitral valve it is no simple matter at times to decide whether the valve is actually stenosed or not. Occasionally the mitral orifice is constricted by a mass of vegetations engrafted on a valve which, although the site of previous injury, is not narrowed. Such conditions may well produce the customary physical signs of mitral stenosis, as occurred in one case in this series that came to autopsy. An analysis of all of our 111 cases showed that in 19 instances the physical signs were such that a diagnosis of questionable mitral stenosis was made. In 8 other instances the evidence was sufficient to warrant a *definite* clinical diagnosis of mitral stenosis. Of the 30 cases that came to postmortem examination 4 showed definite mitral stenosis. In many of the other cases studied at autopsy the mitral valve whether the site of vegetations or not, showed evidence of old rheumatic endocarditis with thickening of the edges of the valve and retraction but no mechanical stenosis. If all the questionable cases are included 24.3 per cent of the cases were diagnosed as having mitral stenosis but only 7.2 per cent were diagnosed as having definite mitral stenosis. The incidence of mitral stenosis in the cases examined at autopsy was 13.3 per cent. Considering the great frequency of mitral stenosis* as a definite finding in cases of

* During the period covered by this study approximately 900 different cases of mitral stenosis were admitted to the Peter Bent Brigham Hospital or were seen by one of us in private practice.

rheumatic valvular disease its occurrence in this series judged by the data obtained either at the bedside or postmortem is quite rare.

The remainder of the cases that made up this series consisted of small heterogeneous groups, of which the most important was that with congenital heart disease. There were 5 such cases, 2 of which were examined postmortem. One of these was found to have vegetative endocarditis engrafted on a patent ductus arteriosus, with vegetations on the aortic and pulmonary valves both of which were bicuspid. In the other, vegetations developed on a bicuspid aortic valve. The importance of congenital abnormalities of the heart as a predisposing factor in the subsequent development of bacterial endocarditis has been emphasized by Lewis and Grant.[11] There were only 3 other cases that have not been discussed, 1 of which was of some interest. This was the only instance in which a definite diagnosis of aortic stenosis was made where no diastolic murmur could be heard. It therefore could not be included among those with aortic insufficiency. In only 1 of the 30 autopsies were vegetations found on the tricuspid valve.

Mention has been previously made concerning the differences of opinion as to the frequency with which various valves are involved in subacute endocarditis. Although most writers have felt that the mitral valve was the most common site for the development of vegetations, others have thought the aortic was more commonly involved. In this series of 30 cases that were examined postmortem, vegetations were found confined to the mitral valve in 8 instances, and to the aortic valve in 8 instances. In 13 cases both were involved, and in 1 case the aortic and tricuspid valves showed vegetations. The inference from this small series is that the aortic and mitral valves are affected with approximately equal frequency.

**Does Organic Mitral Insufficiency Occur?** An interesting and significant sidelight that developed in the course of this study concerns certain data that seem to indicate the existence of regurgitation without stenosis of the mitral valve during life. There has been much written about this subject. Until a short whole ago organic mitral regurgitation was a common clinical diagnosis. Mainly as a result of experiences in the Great War, when large numbers of young men were found to have a slight systolic murmur but no organic heart disease, the pendulum has swung to the extreme opposite position. There is at present a tendency to the view that regurgitation without stenosis of the mitral valve does not exist. With this there has been a growing belief that apical systolic murmurs in the absence of other signs of heart disease are of no significance whatever. In discussing whether mitral regurgitation exists and explaining why this diagnosis is incorrectly made so frequently, Cabot[12] states that "physicians diagnose mitral regurgitation when they hear loud apical systolic murmurs which are extremely common in all sorts of noncardiac disease as well as in health." (P. 290.)

Later (p. 291) he adds that "systolic murmurs without other signs of cardiac disease are of no importance as evidence of valve lesions." Speaking about regurgitation without stenosis of the mitral valve he continues (p. 292) "perhaps in ulcerative endocarditis such a state of things may occasionally exist." In conclusion he states "a diagnosis of mitral regurgitation without stenosis is never justified." (P. 296.) Fully aware of the fact that systolic murmurs occur in a variety of conditions both in which the heart is not diseased at all or in which the valves in particular are normal, we do believe that there is a distinct group of cases showing a moderately loud or a loud apical systolic murmur where this sign is the main evidence of an organic mitral lesion producing mitral regurgitation without stenosis. Such patients are often entirely free from all symptoms and frequently have been refused life insurance because of this murmur. The heart need not be appreciably enlarged and in fact complete examination may be otherwise negative. Commonly a past history or family history of rheumatic fever may be elicited or some other evidences of the rheumatic state uncovered, such as recurrent nosebleeds and the like. At this stage these patients rarely die. Many of them eventually develop mitral stenosis and later die of congestive heart failure. On postmortem examination, therefore those patients, in whom the progress of the disease was not prematurely interrupted and who died of congestive heart failure, will show mitral stenosis. Subacute bacterial endocarditis, however, is just such an event that prematurely cuts short the development of the progressing valve lesion long before there would have occurred congestive heart failure. This enables us to see the mitral valve at autopsy at a stage of incompetency without stenosis. In this series of 30 postmortem examinations there were 6 instances in which the vegetative endocarditis was limited to the mitral valve and the lesion, though producing an insufficiency as evidenced by a mitral systolic murmur in life and pathologic changes at autopsy, did not show mitral stenosis. There were numerous other instances in which only a systolic murmur was known to be present for years antedating the terminal illness. Many of these we regard as having had organic mitral insufficiency with structural changes in the valve, as it is known that subacute bacterial endocarditis almost never develops on previously normal valves. We, therefore, feel that one is justified in making the diagnosis of organic mitral regurgitation in patients showing a moderately loud apical systolic murmur in whom other causes such as hypertension, anemia, and the like are lacking, especially where a past history or family history identify the individual as being rheumatic.

**Previous History of Infections and General State of Health.** It is generally recognized that some history of rheumatic infection is frequently obtained in cases with subacute bacterial endocarditis.

We became interested in analyzing this in greater detail, especially determining the more exact character of this antecedent illness. In this series of 111 cases there were 42 with a history of rheumatic fever alone. There were 3 that only had chorea, and 6 that had both chorea and rheumatic fever. It is striking that chorea, of itself, is so rarely found in the past history of these patients. In 100 cases of rheumatic heart disease, Coombs[13] noted 18 instances in which a history of chorea was the only other rheumatic manifestation. He found 30 instances in which chorea was associated with other rheumatic features such as arthritis or nodes. It follows that in cases of subacute bacterial endocarditis a past history of chorea is obtained much less frequently than occurs with rheumatic heart disease in general. This is in keeping with the above-mentioned conception that mitral stenosis is rarely the seat of subacute bacterial endocarditis, for chorea has a peculiar predilection for the mitral valve producing eventually stenosis of the valve. Strong[14] found that in 45 valvular cases due to chorea the mitral valve was involved in 44 instances, the aortic in 1, and in 4 both were involved.

There were 15 patients who gave a past history of scarlet fever, 3 of whom also had rheumatic fever and 1 had chorea. Scarlet fever seems to be somewhat allied to rheumatic fever as an etiologic factor in producing valvular disease. A careful analysis of the history of patients in whom scarlet fever was supposed to have initiated valvular disease will frequently disclose the fact that in the wake of the scarlet fever there have been vague pains in the limbs. May this not be an associated rheumatic infection? Scarlet fever was the only other specific disease that was commonly found in the past history of these patients.

The question arises whether syphilitic disease of the aortic valves ever serves as the locus for subacute bacterial endocarditis. In this series there were 9 instances with a positive Wassermann reaction. An analysis of these 9 cases discloses that 6 of them also had a previous history of rheumatic fever and another had scarlet fever. In 4 the valvular lesion was mitral insufficiency and therefore syphilitic disease of the valves need not be considered, especially as 3 of these had had rheumatic fever. Likewise another one of these with a positive Wassermann had aortic stenosis which we feel quite sure was not syphilitic, as he previously had had rheumatism. This leaves 4 cases with aortic insufficiency 2 of which had rheumatic fever and 1 scarlet fever. The remaining 1 had Argyll-Robertson pupils and no history indicating a rheumatic infection. This serves as the single instance in the entire series that one might reasonably regard as having had subacute bacterial endocarditis engrafted on luetic aortic insufficiency. One may conclude, as does Thayer[5] that syphilis as a predisposing agent in streptococcus endocarditis is extremely rare.

Of the remaining cases in this series, there were 6 in which the

data concerning the past history were insufficient. There were 2 patients who had no other previous infection except pneumonia and 2 others in which a questionable history of rheumatic fever was elicited. Finally, in 39 cases no history of any significant previous infection could be obtained. We are of the opinion that if more were known about the past history and family history of such negative cases, many of them would have been identified as being rheumatic.

Mention was made earlier in this discussion that many of these patients were singularly free from recurrent rheumatism before developing subacute bacterial endocarditis. Of the 42 cases that had rheumatic fever as the sole predisposing cause, 28 had only one attack, and thereafter were free of rheumatism. The average interval that elapsed between the rheumatic fever and the development of subacute bacterial endocarditis was 17.5 years. This interval varied a great deal, the extremes being 6 months and 44 years. There were 7 others who had 2 bouts of rheumatism. The remaining 7 cases had three or more attacks. It is very difficult to compare these figures statistically with the type of rheumatism that occurs in the larger group of rheumatic heart disease. It is certainly striking, however, that a smouldering rheumatic infection continuing with varying intensity for years that we so commonly see in our heart clinic, was almost never found in the past history of these patients. They generally had one, sometimes two discrete attacks and then there followed a period of freedom and wellbeing until the onset of the bacterial type of endocarditis.

Although there is a sequential relationship between rheumatic valvular disease and subacute bacterial endocarditis in the sense that the latter is generally engrafted on the former; from an entirely different point of view there is also a peculiar antagonism between the two diseases. It has seemed that those who clinically become immune to rheumatic fever are most apt to develop subacute bacterial endocarditis and contrariwise, those who continue with rheumatic manifestations are the least likely subjects. To this clinical conception which we have had for some years there has recently been given certain immunologic support. Whereas cases of rheumatic fever show a very high incidence of positive skin reactions to streptococci or their derivatives (as high as 88 per cent) similarly positive reactions are very rarely found in subacute bacterial endocarditis. Howell and Corrigan[15] found no positive skin reactions to filtrates of streptococci in 7 patients with subacute bacterial endocarditis. Swift[16] had 2 cases with negative reactions, and of 4 of the patients in this present series tested by Derick and Fulton[17] only 1 gave a mildly positive reaction. Furthermore Swift[16] never found a high degree of serum immunity in rheumatic fever patients against the strains of streptococci occasionally recovered from them, whereas patients with subacute bacterial endocarditis are known frequently to have serum of high agglutinating

titer to Streptococcus viridans.[16,18] Finally, Wright[19] was able to produce bacterial endocarditis much more regularly if the animals were previously immunized.

It may be permissible to draw a somewhat speculative and theoretical inference from the above immunologic considerations. There is an apparent incompatibility between the state of susceptibility to rheumatic fever and the simultaneous susceptibility to subacute bacterial endocarditis. It has been shown above that mitral stenosis rarely forms the background for bacterial endocarditis. May one not infer that the progressive development of mitral stenosis is a local evidence of a continued allergic condition in the heart and that the rheumatic state may be persisting even in the absence of limb pains or fever? If this were true it would help to explain the rarity of subacute bacterial endocarditis in patients with mitral stenosis on the assumption that such patients have not developed the immunity requisite for subacute bacterial endocarditis. Furthermore, it may be inferred that any measure which renders a patient immune to rheumatic infections and does away with the allergic state during the early part of the disease may actually serve to prevent the subsequent development of mitral stenosis.

The general health of these cases previous to the development of subacute bacterial endocarditis was analyzed, particularly from the point of view of circulatory efficiency. Libman[2] was interested in a similar aspect of this question and stated that "it is noteworthy that the infection occurred mostly in persons who did not know they had a valve lesion; or knew it but had no symptoms, or slight or moderate symptoms only." Only rough estimates could be made but some general opinion was obtained concerning the ability of our patients to do heavy or light work, whether they had had much dyspnea, and especially whether they had had much heart failure. They were divided into three groups. The first included those who had *excellent* cardiac function. They had no symptoms referable to the heart, and many were even performing very vigorous work. The second were regarded as being in *good* condition, *i.e.*, they had slight dyspnea and palpitation at times but were able to work. The third group we considered as in *fair* health. These had more definite dyspnea but were ambulatory and never had had congestive heart failure. With this arbitrary subdivision it was found that in 76 the circulation was in excellent condition, in 17 it was good, and in 10 it was fair. There were 8 cases in which these data were not available. There were no instances in which congestive heart failure was known to have occurred prior to the development of subacute bacterial endocarditis. It is striking that approximately three-fourths of the patients were in excellent condition and that an additional 15 per cent were regarded as in good condition. A common experience was to learn that the patient was vigorous, able to

do hard physical work, or to play active games like tennis. In general it seemed that the very well compensated cardiac patients with aortic or mitral insufficiency were the ones most prone to develop subacute bacterial endocarditis.

In this connection, a study was made of the previous existence of heart disease, and especially of a heart murmur. Although many of these patients had felt well for long periods of time, they were aware of the fact that someone had heard a murmur in their hearts many years before or they had been told they had heart disease at some previous time. It is more than likely that the diagnosis of "heart disease" in such cases had been made on the presence of murmurs because these cases include practically no instances of angina pectoris, auricular fibrillation or congestive heart failure and only rare instances of hypertension. In 60 of our cases definite information could be obtained concerning the presence of a previous heart murmur or of "heart disease." The average length of time elapsing between the patient's first knowledge of this and the development of subacute bacterial endocarditis was 12.3 years. The shortest interval was 1 year and the longest 45 years. We have no doubt that if we could have examined or questioned all these patients carefully before their final illness, most if not all of them would have shown evidence of valvular disease.

Age and Sex. When the question of age and sex was analyzed in detail, there appeared certain curious relationships. Of the entire series of 111 cases, there were 67 males and 44 females, a proportion of 3 to 2. This corresponds exactly to the proportion found by Blumer.[7] In a study of 762 cases of mitral stenosis[20] the females predominated in a proportion of 2 to 1. The discrepancy in these 2 groups of cases again emphasizes the relative antagonism between mitral stenosis and subacute bacterial endocarditis. The average age of the males with subacute bacterial endocarditis was 35.7 years and of the females 26.9 years. It is rather peculiar that under the age of 20 there were 14 females and only 2 males. In all the succeeding decades (Table 1) the males predominated to an

Table 1.—Age at Death.

| Years. | Males. | Females. | Total. |
|---|---|---|---|
| 11 to 19 | 2 | 14 | 16 |
| 20 to 29 | 23 | 18 | 41 |
| 30 to 39 | 17 | 5 | 22 |
| 40 to 49 | 14 | 3 | 17 |
| 50 and over | 11 | 4 | 15 |

increasing degree so that over 40 years of age there were 25 males and 7 females. This may be explained by the fact that with advancing years the females with rheumatic heart disease are more prone to develop mitral stenosis and are thereby less liable to subacute bacterial endocarditis.

On dividing the cases according to the type of valve lesion present similar differences in the age between the two sexes were found. Of 30 cases with mitral disease alone, there were 14 males with an average age of 37 and 16 females with an average age of 27. Of 42 cases in which the valve lesion was predominantly aortic insufficiency, there were 32 males (average age 35) and 10 females (average age 27). It is rather striking that in the mitral group the females actually predominate, whereas in the aortic group the males outnumber the females 3 to 1. Why it is that subacute bacterial endocarditis is so much more commonly seen in young girls than in young boys remains unexplained unless it is due to the greater prevalence of rheumatic fever in the female in the early years of life.[21] This and other anomalies in age and sex distribution need further elucidation.

Size of the Heart. The average weight of the heart in 29 cases that were examined postmortem was 489 gm. These cases were subdivided into groups according to the site of localization of the vegetations. There were 7 with vegetations limited to the mitral valve. The average weight of the heart in this group was 396 gm. There were 8 in which the vegetations were limited to the aortic valve. The average weight here was 586 gm. There were 12 in which both valves were affected and they averaged 503 gm. The average heart weight of the 2 cases of congenital heart disease was 351 gm. As was expected those cases with only mitral involvement in general had comparatively small hearts, while those with aortic disease showed considerable enlargement.

**Arrhythmias.** It has been noted that irregularities of the heart in subacute bacterial endocarditis are rare.[1,2] In this entire series auricular fibrillation was never found except in one instance as a terminal event. Electrocardiograms were taken in 62 out of 84 hospital patients. There were 2 cases that showed complete heart block and 2 additional ones in which $A$–$V$ conduction was delayed. Premature beats were comparatively rare. Only 2 patients showed ventricular extra systoles and 1 showed both auricular and ventricular premature beats. To be sure, had the patients been examined more frequently, a few other transient arrhythmias might have been noted. The inference to be drawn is that the heart remains essentially regular in subacute bacterial endocarditis and furthermore that if a patient has auricular fibrillation it is extremely unlikely that he has or will ever develop subacute bacterial endocarditis.

Blood Pressure. Little attention has been paid to blood pressure findings in this disease. There were 92 patients in whom blood pressure readings were made. The average systolic pressure was 118 mm. and the average diastolic 52 mm. In order to obviate the effect that aortic insufficiency has on the blood pressure, an analysis was made of the readings of 25 cases in which the mitral

valve alone was involved. In this group the average systolic reading was 110 mm. and the average diastolic 64 mm. The figures differ somewhat from the average of the entire group, for the aortic cases on the whole would show a higher systolic and a lower diastolic pressure than the general average. There were only 4 cases with systolic readings over 150 mm. These were all instances of aortic insufficiency. The low average level of the blood pressure could not be accounted for by the age of the patients, for the average figures of the 15 cases over 50 years of age were systolic 119 mm. and diastolic 56 mm. It may be concluded that hypertension does not occur with subacute bacterial endocarditis except in a few instances in which the systolic pressure may be slightly elevated as a part of the phenomenon of aortic insufficiency. This may serve as an additional point in excluding the diagnosis of subacute bacterial endocarditis in any doubtful case.

Peculiar Onsets. A very extensive review of the mode of onset of this disease was published by Libman in 1918.[2] It is generally understood that the onset of subacute bacterial endocarditis is apt to be insidious. The patients, previously in good health, often begin to have grippe-like symptoms. There may be a sore throat during the early days of the illness but the more striking features are general malaise, weakness, anorexia, vague aches, headache, chills and sweats. During the early days or weeks they are often diagnosed as grip or "rheumatism" and sometimes the possibility of typhoid fever or tuberculosis is seriously considered.

What has particularly interested us in this aspect of the study have been unusual modes of onset that occurred in some of our patients. There were 4 instances in which the patients dated the onset of their symptoms to the extraction of teeth and in 2 others the symptoms seemed to be distinctly aggravated by this procedure. Although it is not absolutely certain that the disease had not already started before the teeth were extracted in the above 4 cases, it is likely that in some of them the operation precipitated the development of the subacute bacterial endocarditis, for they all had previously been feeling well. These experiences make one hesitate in advising the extraction of teeth in cases that are likely subjects for bacterial endocarditis.

Another group included those with a sudden onset of pain in the back, as the major complaint. Embolic manifestations producing sudden pain in the fingers, toes and limbs have been well recognized phenomena in this disease. A similar sudden pain in the side or back, generally unilateral, as an evidence of emboli to the kidney or spleen, has not been sufficiently emphasized as an early feature. There were 5 cases in this series in which sudden fairly severe pain in the back was the earliest distressing symptom. In 1 such case because the back pain was associated with gross hematuria and dysuria, the diagnosis of renal stone was incorrectly made for a

while. Careful questioning of this patient revealed that although he had been working until this pain occurred he had been losing weight and strength for more than a month. Similar information no doubt could be obtained in many cases antedating what was regarded as the major complaint. The importance of these observations is that subacute bacterial endocarditis must be thought of in patients complaining of sudden pain in the back if there are any other features like fever and a heart murmur that make this diagnosis at all possible.

Several other cases showed most unusual types of onset. In 2 the earliest symptoms were mental, with the development of definite psychoses. One of these was first seen by us in a psychopathic hospital. In another case the disease seemed to develop after a pelvic operation for bilateral salpingitis. A fourth had had a well compensated valve injury for years and had been doing strenuous work every day until he developed an apparently minor infection of the foot, as the result of stepping on a nail. From then on he ran a typical course of subacute bacterial endocarditis. No doubt with more extensive experience we will find other peculiarities in the mode of onset of this disease.

**The Evaluation of a Systolic Murmur as an Aid in Diagnosis.** It is not the purpose of this discussion to go into the details of the diagnosis of subacute bacterial endocarditis. Apart from the swinging temperature and the prodromal symptoms mentioned above, there are numerous findings occurring at one time or another that are sufficiently distinctive to enable one to make a presumptive diagnosis. These are enlargement of the spleen, clubbing of the fingers, sudden peculiar pains in the finger tips, showers of red blood cells in the urine, and characteristic rose-colored oval petechiæ, most commonly seen in the conjunctivæ. Of course finding streptococci in the blood stream by cultural methods serves as an important decisive confirmation of the diagnosis. However, there are instances in which none of the above findings occur for intervals of time, and as happened in several instances in this series, the first clue to the diagnosis arose from the proper evaluation of a systolic murmur. Because such a murmur is so frequently regarded as insignificant, little attention is paid to it when the symptomatology suggests some noncardiac conditions. Particularly is this true when the patient is known to have had the murmur for years. On the other hand it is just this sort of a patient with a well compensated heart showing a murmur for years who should always be suspected of having subacute bacterial endocarditis if he develops fever and vague or unexplained symptoms. As an illustration one of our cases was a woman, aged 55 years, who complained of general fatigue of 2 months' duration. During this time she had lost 18 pounds in weight, had had occasional headaches, a slight cough and complained of vague pains in the abdomen and left shoulder. There was a history of rheumatic

fever in childhood. Physical examination was entirely negative except for slight fever and a moderately loud systolic murmur. A presumptive diagnosis of subacute bacterial endocarditis was made which was confirmed by the subsequent development of typical petechiæ and the finding of Streptococcus viridans in the blood stream. Another example was the patient cited above who came into the hospital with the diagnosis of renal stone, because of sudden pain in the left loin, dysuria and gross hematuria. Physical examination was essentially negative except for a loud apical systolic murmur. In fact at the time we saw him there was no fever. Because the systolic murmur remained unexplained on the basis of the diagnosis of renal stone, we questioned him more carefully and elicited the other vague symptoms that had preceded the attack of pain by a month or two. In both of these instances, as well as in others not detailed, it was the systolic murmur which first focussed our attention on the correct diagnosis.

TREATMENT. There is hardly a disease in which a greater variety of treatments has been tried than subacute bacterial endocarditis. Most observers are in accord with the belief that specific therapy is valueless. A few, however, feel that injections of sodium cacodylate have caused recovery. In our experience all the various therapeutic procedures employed have proved fruitless. We wish to record several instances in which novel methods of therapy were tried which also were ineffective. The general purpose of these procedures was the attempt to alter the immunologic state of the patients in some such way as occurs in the thermal treatment for general paresis or the nonspecific protein therapy in chronic arthritis. Two of our cases were deliberately given rat-bite fever. One other was injected with blood from a patient suffering from malaria. This case, however, did not develop malaria. A Bier operation[22] was performed on a fourth patient. This consisted of cauterizing a large area under the left breast. This patient and 3 others were also given 1 or more subcutaneous injections of turpentine for the purpose of producing a sterile abscess. Although in one of these latter cases, the temperature promptly fell to normal and remained so for more than a month, no real benefit was derived from any of these methods. (Two other cases, not included in this series were given typhoid vaccine intravenously, in 1 of which at least a temporary disappearance of the fever was obtained.) Knowledge concerning the pathology and diagnosis of subacute bacterial endocarditis is extensive, but treatment except for hygienic care, is at present of no avail.

**Summary.** 1. A clinical study has been made of 111 cases of subacute bacterial endocarditis. Thirty of these were examined postmortem.

2. It is generally conceded that Streptococcus viridans endocarditis becomes engrafted on previously damaged valves. In spite

of the great frequency of mitral stenosis as a type of chronic valvular disease, it was found to be associated comparatively rarely with subacute bacterial endocarditis. Only 7 per cent of these cases showed definite clinical evidence of mitral stenosis and 13 per cent of those examined postmortem had mitral stenosis.

3. There were 23 instances of mitral insufficiency (showing a systolic murmur alone) and 66 of aortic and mitral insufficiency, 10 of which had signs of aortic stenosis as well. There were 5 with congenital abnormalities of the heart and the remainder consisted of small heterogeneous groups.

4. On postmortem examination vegetations on the valves were found as follows: mitral alone 8; aortic alone 8; both 13; aortic and tricuspid 1.

5. As a result of this study the following general rules may be formulated:

(*a*) If no murmur whatsoever is heard over the heart, one can practically dismiss the diagnosis of bacterial endocarditis.

(*b*) If only a systolic murmur is heard the vegetations will be found limited to the mitral valve and adjacent endocardium. (This excludes the rare cases of congenital heart disease.)

(*c*) If there is in addition to a systolic murmur a basal diastolic murmur, one may predict that there are vegetations on the aortic valve and that there may or may not be a similar lesion on the mitral valve.

6. A previous history of some definite rheumatic infection was obtained in 51 instances. Forty-two had rheumatic fever, 3 had chorea, and 6 had both. From an analysis of the degree and duration of rheumatic infection from which these patients suffered, they were found as a group to have been comparatively free from this type of infection for a considerable period of time preceding the development of subacute bacterial endocarditis. Twenty-eight of the 42 patients who had had rheumatic fever had had only a single attack. In these there was an average interval of 17.5 years before subacute bacterial endocarditis developed. It is our opinion, based on this clinical study and other immunologic data that the immunity to rheumatic infection developed in these patients, renders them more susceptible to subacute bacterial endocarditis.

7. A study of the past history of these patients from the point of view of ability to work and of circulatory efficiency, showed that the cardiac condition could be regarded as "excellent" in 76, "good" in 17, and "fair" in 10. There were no instances in which congestive heart failure was known to have occurred prior to the development of subacute bacterial endocarditis, though there was satisfactory evidence that in 60 cases heart murmurs had been present for a period of years. It is believed that had we been able to examine

these patients shortly before the development of subacute bacterial endocarditis most if not all of them would have shown a murmur.

8. The following are some of the other findings of interest in this study. The males outnumbered the females 3 to 2. The average age of the males (35.7) was 9 years greater than that of the females (26.9). The average heart weight in the autopsied cases was 489 gm. Significant arrhythmias were rarely found. Only 1 case showed auricular fibrillation and that as a terminal event. The average blood pressure in 92 patients on whom readings were obtained was 118 systolic and 52 diastolic. There were only 4 cases with a systolic pressure over 150 (all of whom had aortic insufficiency) indicating that hypertension is extremely rare in this form of heart disease. There were cases with very peculiar types of onset in which the evaluation of a systolic murmur was a most important clue to the diagnosis.

9. Several novel but ineffective methods of treatment were employed in some of these cases such as the production of rat-bite fever and malaria, typhoid vaccine intravenously, sterile turpentine abscesses, and cauterization of the breast (Bier method).

10. The patient who is most apt to develop subacute bacterial endocarditis is one who has had a mitral systolic or an aortic diastolic murmur for some years. If he gives a history of previous rheumatic infection, as happens in about half the cases, it is most likely to be of a single attack with unusual freedom from recurrences. He has been able to carry on essentially normal activities, has shown at no time any important irregularities of the heart or evidence of congestive heart failure, and has either a low or normal blood pressure.

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## SARCOMA OF THE SPLEEN.

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Primary sarcoma of the spleen is a rather uncommon disease. The frequency of its incidence may be shown by the fact that of 40,000 surgical cases at the Boston City Hospital only 2 cases of primary malignancy of the spleen were noted. Two cases of primary splenic malignancy are reported from the Mayo Clinic, and at the Massachusetts General Hospital the diagnosis of malignancy of the spleen has been made but four times and of these only 1 was proven by operation.

Smith and Rusk[1] have collected 104 cases of malignancy of the spleen and add 2 of their own. These 2 cases were endotheliomata, the growth arising from the sinuses of the organ. It is the opinion of these observers that lymphosarcoma is probably the commonest type and is usually part of a generalized process, appearing at the same time or later in other lymphatic structures. Since the paper by Smith and Rusk other cases have been added to the literature by T. Howard,[2] Ladreyt, Debrym, Beasley, Berman, Kohler, Adam, Eichenbusch and Krumbhaar,[3] who added 4.

Krumbhaar states that the predominant symptom of malignancy of the spleen is splenomegaly. Pain in the left side or back and in the left shoulder, together with tenderness, is often present. Indigestion with flatulence and constipation is frequently noted. There may be a marked secondary anemia, and jaundice and anasarca are

occasionally seen, as is also fever and leukocytosis. The diagnosis is made on the rapidity of the growth and the exclusion of other causes of splenic enlargement.

Splenectomy is the only curative treatment and was successful in 21 of 39 cases collected by Smith and Rusk. Of the 18 deaths 7 resulted from the operation and 11 were due to recurrences.

The first case which we wish to report was operated upon by Dr. Guy P. Grigsby, and we thank him for the courtesy of permitting us to include his case in this report.

**Case Reports.** CASE 1.—C. R. J., white, aged 34 years, seen in August, 1927, gives the history of having had digestive upsets since the autumn of 1926, and in the past few weeks has become weaker and lost 15 pounds in weight. About 3 weeks ago he thought he had pleurisy and his chest was aspirated and 10 cc. of fluid removed. He has had no previous serious illness and his family history is entirely negative. The patient is undernourished; the mucous membranes show moderate pallor. The skin is atonic and clear of eruptions. The muscles are flaccid. The appearance is that of subnormal strength and energy, but not of physical distress. The tongue is furred, moist and rather pale. The eyes are negative. The capillary circulation is subnormal. The heart action is regular, rhythmic; the valve sounds are pure, except for a very faint systolic blow over the mitral area, transmitted toward the pulmonic area. The stomach is displaced toward the right on account of a mass, the gastric percussion note being elicited to the right of the midline, a distance of about 2 inches, with the greater curvature 2½ inches below the umbilicus. The liver is enlarged, palpable, smooth, of slightly increased firmness and measures 5 inches in right mammary line. The abdomen is asymmetric, the left side being larger than the right. The walls are thin, superficial veins distinct, with dilatation of the capillaries overlying the diaphragm to a moderate degree. On palpation, a mass is felt on the left side extending to nearly a level with the umbilicus and, reaching across the midline, continues under the free costal margin. A distinct notch can be felt on its lower border. It is fairly smooth, quite firm, slightly tender, fills the left flank and is palpable in the left lumbar region. Below the sixth and seventh costal margins the mass shows a prominence which is palpable and appears to be firmer than the remainder of the structure. There is a question about fluid in the pleural cavity. The chest is fairly well developed, respiratory movements rather shallow but regular. The right lung shows no definite pathology. The respiratory sounds are a bit harsh. The percussion note is unmodified and the vesicular murmur is heard over the entire lung. The left lung shows a similar condition except for some modification of the percussion note and râles over the base posteriorly. The left diaphragm is situated high on account of the mass in the abdomen and shows practically no range of respiration. The patient is mentally clear, with good memory. The speech is deliberate, but there are no defects. The reflexes are normal, superficial and deep. No ataxia or incoördination of gait is present. The hearing is normal.

Laboratory studies showed: Urinalysis, negative. The blood count on August 25, 1927, was: Red cells, 3,790,000; leukocytes, 6800; hemoglobin, 75 per cent; color index, 0.9; polymorphonuclears, 74 per cent; small lymphocytes, 15 per cent; large lymphocytes, 10 per cent; eosinophils, 1 per cent; basophils, 0. Morphology: Poikilocytosis, increase in blood platelets. August 29, 1927: Red cells, 4,970,000; leukocytes, 13,850; hemoglobin, 90 per cent; polymorphonuclears, 76 per cent; small lymphocytes, 20 per cent;

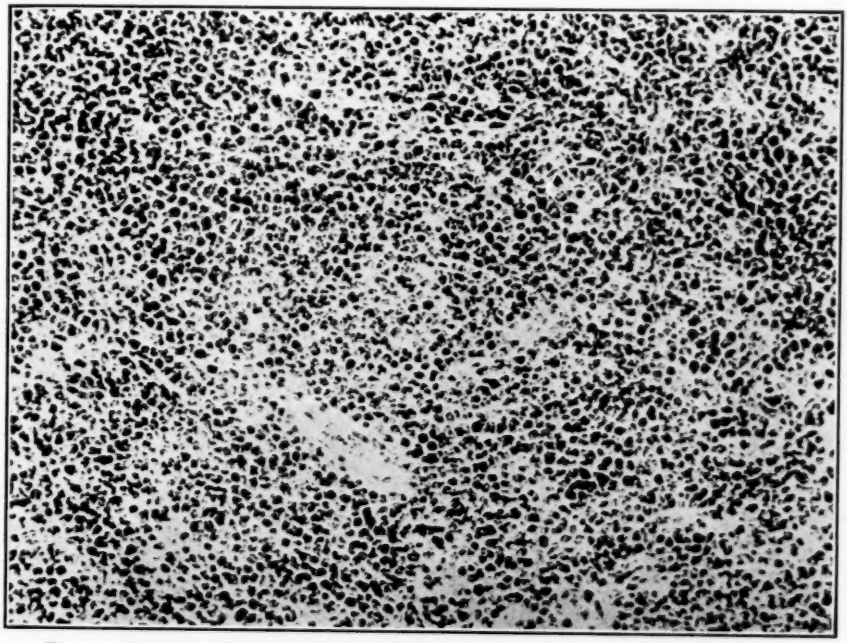

FIG. 1.—Case 1. Shows marked proliferation of lymphocytes with obliteration of normal splenic marking. Magnified 24 diameters.

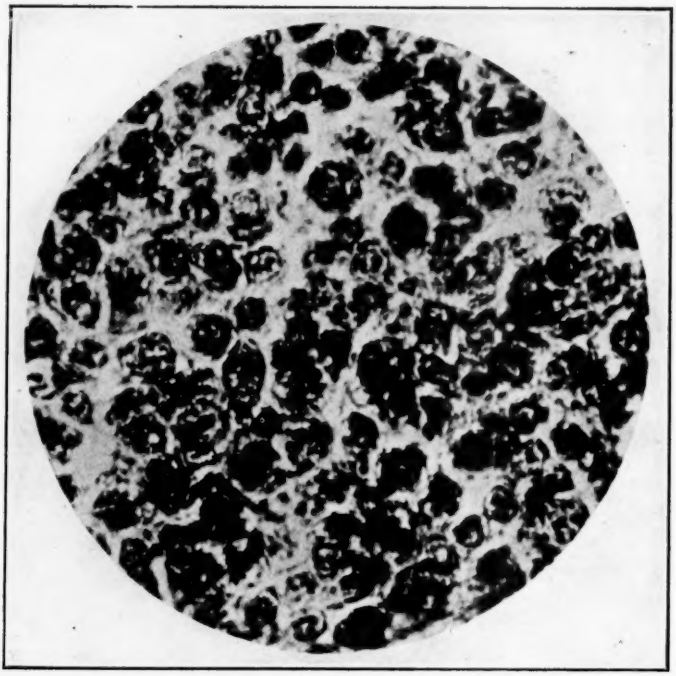

FIG. 2.—Case 1. Illustrates small amount of supportive tissue and marked rapidity of proliferation as shown by numerous mitotic figures. Magnified 900 diameters.

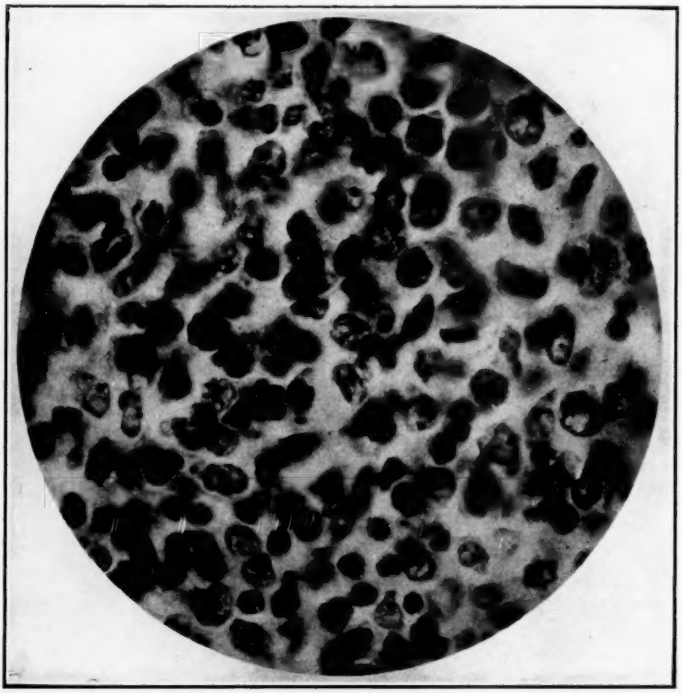

FIG. 3.—Case 2. Shows very little stroma. Marked proliferation as shown by numerous mitotic figures and appearance of diasters. Magnified 900 diameters.

eosinophils, 4 per cent. September 8, 1927: Leukocytes, 19,400; hemoglobin, 80 per cent; polymorphonuclears, 79 per cent; small lymphocytes, 15 per cent; large lymphocytes, 4 per cent; eosinophils, 3 per cent. Morphology: Increase in blood platelets.

The blood picture during the period of hospitalization changed rather rapidly and very definitely. The appearance of transitionals, lymphoblasts, eosinophilic leukocytes, large mononuclear leukocytes and an increasing anisocytosis being observed.

Gastric analysis showed slight retention but the chemical study revealed no abnormalities.

On December 5, 1927, after a transfusion of 500 cc. of citrated blood, the patient was operated upon by Dr. Grigsby. A right rectus incision was made and the abdomen opened, disclosing a large tumor that was densely adherent to all the surrounding structures, including liver, stomach, transverse colon and small intestine. The tumor had a nodular appearance, the upper portion being more or less solid and the middle being a large cyst. Enough of the adhesions were freed fully to expose the tumor and, as its appearance was suggestive of malignancy and it being so adherent to other important viscera, its removal was thought impossible. Palpation of the tumor caused considerable bleeding, particularly at the attachment of liver. A hot sponge placed on it controlled this and the abdomen was closed in the usual manner.

Following operation, he rapidly went into shock and died 24 hours later.

An hour after death the wound was reopened and further examination of the condition was made. The cyst was opened and found to obtain about 1 liter of rather thin grumous fluid that had the appearance of pus but was odorless and believed to be the result of a hemorrhage into the cyst. The adhesions to the surrounding viscera were even more dense than they were thought to be at the time of operation. The upper portion of the tumor was partially solid, the center of it being filled with broken-down colloid-looking material. The lower portion of the tumor had invaded the mesentery of the transverse colon and one projection of it extended over to the cecum. This portion of the tumor seemed of more malignant nature than any portion examined. A large specimen was taken from this and also the upper portion of the tumor. The spleen was exposed, the notch plainly seen and the lower pole appears normal in consistency and size. The upper portion of the spleen was enlarged four or five times its normal size and firmly adherent to the parietal peritoneum. As much of it as was exposed seemed of normal appearance, with the exception of hypertrophy.

The free border of the right lobe of the liver was very thin and extended about four fingerbreadths below the costal margin. The rest of the liver from palpation appeared very much atrophied and was very hard. This examination plainly showed the futility of any operative removal of the growth and there was little doubt of its malignant character.

Microscopic study of removed sections by Dr. Stuart Graves revealed atypical masses of cells, apparently of lymphoid origin. These cells varied greatly in size and shape. There was little connective-tissue stroma. There were numerous mitoses. (Figs. 1 and 2.)

*Microscopic Diagnosis:* Lymphosarcoma.

CASE 2.—Mrs. R. C. C., white, aged 30 years, was first seen by us in April, 1927. She had had 3 children and 1 miscarriage 3 years ago. Other than the fact that her father had died of pulmonary tuberculosis, the family history was negative. The present illness began in December, 1926, with sharp pains in the left hip and leg which continued for a month. She then developed pain in the left upper extremity and also in the right upper and lower extremity. There was never any swelling or redness of the joints and very little occasional stiffness of the extremities. There has

never been any elevation of temperature. The tonsils were suspected as the cause of her trouble, and removed, without improvement in her general condition. There have been no other symptoms except amenorrhea for 3½ months. The pains in the extremities continued and she visited one of the "spas" without benefit.

Examination shows a markedly undernourished white female whose skin has a somewhat yellowish tint. The mucous membranes are very pale. The eyes, teeth and throat are negative for any abnormalities, the tonsils being out. The thyroid is not enlarged and there are no enlarged lymph nodes in the neck. The breasts are flabby and contain no tumors. There are no glands in the axilla. The lungs are resonant throughout and there are no adventitious breath sounds. The heart is not enlarged. The apex beat is within the nipple line; there are no thrills or murmurs and the sounds are of fair quality. The abdomen is relaxed. The liver is enlarged, extending 1½ inches below the costal margin. It is smooth and firm and not tender. The spleen extends 2 inches below the costal margin and descends on inspiration. There are no other masses and no tenderness.

Gynecologic examination reveals a markedly relaxed pelvic floor, but no other abnormalities. The glands in the groins are possibly a little enlarged. Reflexes in both legs are active. There is no disturbance of sensation in legs.

Laboratory studies showed: Urinalysis, negative. Blood Wassermann, negative. The blood count was: Hemoglobin, 25 per cent; red cells, 1,550,000; leukocytes, 3350; polymorphonuclears, 55 per cent; lymphocytes, 40 per cent; endothelial cells, 5 per cent. Anisocytosis and poikilocytosis were very evident. Nucleated red cells were present. The stool was negative for blood or parasites on repeated examinations. Roentgen ray examination of the gastrointestinal tract was negative. Dental films showed one area of questionable infection.

On April 5 and again on April 8 blood transfusion was done, giving 600 cc. the first time and 500 cc. the second time, using the Vincent tube method.

The blood count on April 9, 1927 was: Hemoglobin, 55 per cent; red cells, 2,950,000

Pains in the legs were not so severe. The patient had some elevation of temperature.

The blood count on April 12, 1930 was: Hemoglobin, 55 per cent; red cells, 3,310,000; leukocytes, 2800; polymorphonuclears, 57 per cent; lymphocytes, 41 per cent; endothelial cells, 2 per cent; icterus index, 7.5; coagulation time, 4 minutes; bleeding time, 3 minutes; blood platelets, 244,000.

The patient was seen by Dr. Morris Flexner, of Louisville, and a diagnosis of early Banti's disease was made and splenectomy decided upon.

A preliminary transfusion of citrated blood was given and splenectomy done on April 18, 1927. The spleen was about three times the normal size, firm and adherent at the upper pole and also posteriorly. It was freed and delivered and after ligation of the pedicle was removed. A gauze strip was packed into the splenic fossa to control oozing. The patient left the table in mild shock.

The following day another transfusion was given after which improvement was marked. The blood count on April 26, 1927 was: Hemoglobin, 63 per cent; red cells, 3,620,000; leukocytes, 2900; polymorphonuclears, 52 per cent; lymphocytes, 41 per cent; endothelial cells, 6 per cent; eosinophils, 1 per cent.

Examination of the spleen by Dr. Stuart Graves was reported as follows: Specimen consists of a spleen, 17 by 10 by 5 cm.; weight, 450 gm.; beefy red and fairly flabby; capsule taut. A series of paraffin sections, thin and carefully stained, show obliteration of normal landmarks with diffuse

atypical growth of undifferentiated, large, hyperchromatic cells of lymphoblastic type with numerous mitoses.

*Microscopic Diagnosis:* Lymphosarcoma.

The patient did not recover her strength as she should have, although the wound healed perfectly. She continued to have pains in the legs and irregular fever. The day before she left the hospital the blood count was: Hemoglobin, 50 per cent; red cells, 3,390,0000; leukocytes, 2140; polymorphonuclears, 39 per cent; lymphocytes, 54 per cent; endothelial cells, 3 per cent. Nucleated red cells (normoblasts), 7. Myelocytes, 4; red cells show achromia and some poikilocytes and a few microcytes.

The patient died 8 months after her operation. No autopsy was done.

This case is interesting, especially in its resemblance to pernicious anemia, because of the high color index, the leukopenia and the increase in the icterus index. The pain in the extremities also suggests pernicious anemia in which cord symptoms are not uncommon.

Howard's case is similar to this one in some respects and varies only in that in his there seemed to be a remission with later exacerbation of symptoms. His case was a recticulated-cell sarcoma and the one we report a lymphosarcoma.

**Summary.** 1. We have herein added 2 cases to the literature of sarcoma of the spleen, both being cases of the lymphocytic type.

2. Sarcoma of the spleen may simulate pernicious anemia in its symptomatology and hemocytology.

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## CHEMICAL FACTORS REGULATING BLOOD PRESSURE.*

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The study of chemical substances capable of elevating or of lowering blood pressure is of obvious importance. The isolation and identification of substances in the body which have hypertensive action may lead to a solution of the etiology of essential hypertension, a disease which still remains, in spite of the enormous amount of study expended upon it, a disease of theories. The isolation and identification of substances in the body which have a hypertensive action may lead, we hope, to a satisfactory control of this same disease, which remains also not only a disease of theories but a disease whose mastery is one of the outstanding challenges of today.

* Read at the annual meeting of the American Climatological and Clinical Association, Hot Springs, Va., May 7, 1931.

As we survey the field we cannot but be impressed by the fact that our knowledge of hypotensive substances is more extensive than our knowledge of hypertensive substances. Indeed, I think one may say without contradiction that, while the presence of several substances in the body capable of lowering blood pressure has been established, and such substances have been isolated, yet the only substance having a hypertensive action whose presence in the body has been definitely proved is adrenalin.

The theory that an excess of adrenalin is responsible for the production of arterial hypertension dates from the observations of Neusser,[17] in 1898, and of Vaquez,[21] in 1904. Vaquez has championed the theory that hypertension is due to an overactivity of the adrenals. In spite of all the work which has appeared in support of this idea, it still remains a theory, since no one has yet proved conclusively that there is an excess of adrenalin in the circulation of patients suffering from arterial hypertension.

In 1922 Labbé, Tinel and Doumer[10] reported a case of arterial hypertension in which a tumor of the adrenal was found at autopsy. Vaquez and Donzelot, in 1926, described a case of paroxysmal hypertension, which was later treated by Laubry with deep Roentgen ray over both adrenals with apparent recovery. Oppenheimer and Fishberg[18] reported, in 1924, a case of hypertension in a young girl, aged 12 years, who showed an adrenal tumor at autopsy. Oberling and Jung, in 1927, described a similar case. Pincoffs,[20] in 1929 reported a case of paroxysmal hypertension who was operated upon by Dr. Arthur Shipley and a tumor of the right adrenal removed. One year later the patient was apparently in perfect health and had a systolic blood pressure of 110 to 125. The tumor proved to be a paraganglioma and contained large amounts of adrenalin.

These observations are of extreme importance since they prove that one type of hypertension is due to an excessive production of adrenalin. However, the symptomatology and clinical course of these cases of paroxysmal hypertension is so characteristic and so different from that of the classical picture of chronic essential hypertension that it is taking a long jump to assure that the two conditions are due to the same etiologic factor.

Next to adrenalin, attention has been directed to certain amines as possible causes of hypertension. Several investigators, notably Koessler, have shown that certain amines may be produced by bacterial decomposition of proteins. This has, of course, inevitably led to speculations regarding the absorption of such products from the intestinal tract with a resulting hypertension. One substance, tyramin, has been studied particularly. Tyramin produces a marked elevation in blood pressure and is absorbed readily from the intestinal tract. Its presence in the body has not, however, been conclusively demonstrated, although the recent discovery by

Hare[7] of a ferment in the liver capable of destroying tyramin is of great interest. The presence of tyraminose in the liver suggests a possible mechanism by which this pressor substance absorbed from the intestinal tract is destroyed and rendered innocuous. Further work along these lines may lead to important discoveries.

We have been interested for several years in a study of guanidin compounds, some of which, as is well known, are powerful pressor substances, while others are equally potent depressor substances. Our observations have been mainly upon guanidin and methyl guanidin, which are pressor substances, and upon glycocyamin (guanidin acetic acid), which is a depressor substance.

In 1927 Weber and I[12] found that in a series of cases of essential hypertension that approximately 50 per cent showed an increase in the blood of some substance giving a color reaction for guanidin. These observations were confirmed by Davis,[3] in 1928, and more recently, in 1930, by Pfiffner and Myers.[19] We have now observations upon more than 400 patients with the same results.

Even more striking are our results in cases of chronic nephritis. We have never yet seen a case of chronic nephritis with hypertension, who failed to show an increase in this substance.

In spite of repeated attempts we have not succeeded in proving positively that the substance producing the color reaction is guanidin, and this failure is, of course, a strong argument against the entire conception. One fact, however, is very striking and difficult to explain away—we have never encountered an increase of this substance in the blood of a person with a normal blood pressure.

The question whether any guanidin compounds other than arginin, creatin and creatinin occur in the body has been hotly debated. Most of the methods employed up to this time to isolate guanidin and methyl guanidin are untrustworthy. It is comparatively easy to obtain methyl guanidin from the urine and muscle, but the methods employed use silver salts, which convert creatinin into methyl guanidin, and such methods are now rightly considered faulty. More recently Komarow[9] has asserted that by using a method free from these objections he has demonstrated the presence of considerable quantities of methyl guanidin in the muscles. This work lacks confirmation as yet, but if correct, is obviously a very important contribution to the subject.

In 1928 we showed that many patients with arterial hypertension whose kidney function when tested by the usual methods is apparently normal, are unable to excrete methyl guanidin in the way that healthy individuals do.[14] These observations have since been confirmed and extended in our laboratory. Their significance is not altogether clear. They may suggest, of course, that such individuals have a peculiar physiologic anomaly of the kidneys, which consists in an inability to excrete methyl guanidin normally. Such an anomaly could obviously lead to a retention of methyl guanidin

with a resulting hypertension. On the other hand, this inability to excrete methyl guanidin may be merely a very delicate test of early renal insufficiency, since in chronic nephritis inability is much more marked and striking than in what we term essential hypertension. More observations over a longer period of time are necessary before we can begin to draw conclusions.

When we turn to a consideration of the depressor substances present in the body we find that a larger group have been definitely isolated and identified and still others are either isolated or their presence strongly suspected. This particular phase of the subject has been followed with intense interest not only by pharmacologists, but particularly by internists who have hoped that some of these substances might prove effectual agents in the control of arterial hypertension.

One of these substances, histamin, has been the subject of a great deal of investigation. The observations of Abel and Kubota, of Koessler and of Dale and his associates have been of great importance. This exceedingly powerful and also highly toxic substance we now know, thanks to labors of Dale and his coworkers, is present in most of the tissues of the body, not merely in traces, but in considerable quantities. The significance of this fact is not fully understood, but the pharmacologic antagonism of histamin to adrenalin suggests a possible normal mechanism of blood pressure control. As a therapeutic agent, however, for the control of high blood pressure histamin is disappointing. It is a highly toxic substance, it reduces blood pressure too rapidly with frequent distressing symptoms and it also has the effect of often being followed by a subsequent rise in blood pressure above the initial level.

Another substance which has a profound depressor effect upon the blood pressure is cholin, whose presence in the body has been definitely demonstrated. More recently another closely allied substance, acetocholin, was isolated by Dale and Dudley.[2] Acetocholin is an extremely powerful depressor substance, being approximately one thousand times as powerful as cholin. Acetocholin is relatively unstable and, while its presence in the body was suspected for some time, it remains for Dale and Dudley to demonstrate its actual occurrence. The isolation of this substance is a striking proof of the skill an ingenuity of these investigators. Drury and Szent-Gyorgi[4] found that adenylic acid and adenosin caused a fall of blood pressure. Adenylic acid is present in the blood in skeletal muscle, in heart tissue, in the brain and in the kidneys.

Glycocyamin, or guanidin acetic acid, is a very interesting substance. It differs from creatin only in the absence of a methyl group, and while creatin has no characteristic effect upon the blood pressure, glycocyamin is a powerful depressor substance. It

is relatively nontoxic, it is effective when taken by mouth and it also, as Ginsberg and Stoland[5] have shown, causes a marked increase in coronary flow. The presence of glycocyamin in the body has not been demonstrated, although Karashima[8] has recently described a ferment in the liver capable of oxidizing it.

Our especial interest in this subject of depressor substances began with the study of the depressor effect of certain liver extracts. We feel that the effects of these extracts was not due to either histamin or cholin, but the evidence was not conclusive. In 1927 Best, Dale, Dudley and Thorpe,[1] in a series of investigations, isolated histamin in considerable quantities from these liver extracts, and were inclined to attribute their depressor effects to the presence of histamin. Vincent and Curtis[22] questioned these conclusions, but since Dale and his coworkers had definitely isolated histamin, and their critics could produce no other depressor substances, the prevailing opinion was that these extracts owed their activity to histamin. We have continued our investigations of this problem the past 4 years and feel that we have definite evidence of the existence of a depressor substance in the tissues which is neither histamin, cholin, nor acetyl cholin. In 1929 Weber and I[16] showed that when liver tissue was treated in two different manners an extract having the pharmacologic properties of histamin could be obtained from one fraction, while from another fraction an extract could be isolated which showed no chemical tests for histamin and also differed in its pharmacologic behavior.

Histamin, as is well known, produces a fall of blood pressure when injected intravenously into dogs, but under certain standard conditions causes a rise of blood pressure in rabbits. One of our extracts which gave a positive Pauly reaction for histamin produced a rise of blood pressure in rabbits, while the other extract which gave a negative Pauly reaction caused a fall in blood pressure in these animals. When these two extracts were mixed in proper proportions and injected into rabbits no change in blood pressure occurred. This latter observation cleared up a question that had puzzled us for a long time—why certain liver extracts produced a marked fall of blood pressure in dogs, but had no effect upon the blood pressure of rabbits.

Later we found this histamin-free depressor substance present in considerable quantities in the brain and we have employed the brain as the source of supply for most of our later experiments. By a process of precipitation with acetone and purification with copper and mercury we have obtained a thick viscid fluid, which is apparently the active principle. When precipitated under certain conditions it comes down as a fine white granular crystalline-like substance, which, however, probably because of its marked hygroscopic properties, is changed almost immediately into a thick oily-like liquid. It is, however, apparently not an oil, for it is insoluble in the ordinary oily solvents.[15]

This substance we have found present in considerable quantities in the blood. This finding we think is of interest since it suggests that it may play a rôle in maintaining the blood pressure at a proper level, since its absence or presence in insufficient amounts could conceivably lead to an elevation in blood pressure. Another finding of some interest is the presence of a positive Sakaguchi reaction in the purest solutions we have obtained, indicating the presence of a guanidin compound.

We have as yet made no extensive studies of the therapeutic effects of those pure histamin-free extracts. We only know that when injected they produce a temporary fall of blood pressure in normal individuals and in certain hypertensives.

This summary of certain chemical factors having hypertensive and hypotensive action, indicates that much information has been obtained and still more is desirable. The whole subject is one of great interest, and it requires great self control not to wander off into a maze of speculation. But as we survey the history of the many diseases which we now understand fairly clearly, we are struck, I think, by the fact that it is one thing to observe, but quite another to interpret.

**Conclusions.** The only pressor substance whose presence in the body has been demonstrated without any doubt is adrenalin. Guanidin compounds capable of elevating the blood pressure may exist in the body, but their presence has not been unequivocally demonstrated. There is some evidence that they are actually present but more proof of their existence must be given before we can definitely state that such is the case.

Several depressor substances have been demonstrated in the body. Histamin, cholin, acetocholin, adenylic acid and adenosin have been definitely isolated. There is in addition another substance with powerful depressor action which has not been identified but which is apparently widespread in the body.

The physiologic rôle of these depressor substances offers a wide field of research. Their possible therapeutic effects, either singly or in combination may open up a new field of therapeutic endeavor.

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## THE STUDY OF YELLOW FEVER BY A PROTECTION TEST IN MICE.

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The prevalent idea about yellow fever seems to be that it has been banished from most of the world and will soon be extinct. The studies of the International Health Division of the Rockefeller Foundation now under way in West Africa and South America show that this view is overoptimistic and that long campaigns will have to be waged before the disease is conquered in the endemic areas of these countries. In the meanwhile, the danger in the situation is being accentuated by the increase of commerce with the endemic regions, the greater rapidity of travel by land, sea, and air, and the rising susceptibility of the population in the regions which have already been freed of yellow fever. On the bright side of the picture is our greater power to control the disease owing to the improvement in methods of diagnosis and of epidemiologic study made possible by the availability of experimental animals.

The regions in which yellow fever is persisting are so vast that indiscriminate intensive control measures throughout the whole of the suspected regions, with their many port cities and populous interior centers, would seem at present to be impossible. It is conceivable, however, that the disease could be suppressed if control efforts could be concentrated in the permanent endemic centers. It has not been possible to locate the endemic regions accurately with the older methods of clinical observation.

In endemic areas epidemics are infrequent, or absent, and only an occasional case, usually in a foreigner, comes to the attention of the authorities. The disease is kept alive in children who suffer with so mild a form that a clinical diagnosis of yellow fever is rarely possible. It is unfortunately true that in most such regions there are almost no well-trained physicians and reliable reports can scarcely be expected. The situation seems to be similar to that revealed in parts of the United States with regard to poliomyelitis by Aycock, Kramer[1] and others.

The bright points in the recent history of yellow fever are: (1) The demonstration by Walter Reed and his colleagues in Havana in 1901, that the disease was conveyed by the *Aëdes ægypti* and that the causative organism behaved like a filtrable virus; (2) the demonstration by Stokes, Bauer and Hudson[2] in West Africa in 1927 that the common monkey of the zoölogical gardens, *Macacus rhesus*, was susceptible to the disease, and (3) the finding of Theiler[3] in 1930 that a neurotropic strain of the virus could be produced by intracerebral inoculation of white mice, so that we now have two susceptible animals.

An effective method of delimiting the endemic areas of yellow fever is to collect the sera of adequate numbers of children at key places and to test these for power to protect experimental animals against yellow fever virus. This has been done for several centers in West Africa by Beeuwkes, Bauer and Mahaffy[4] who used rhesus monkeys. The tests showed a wide variation in the percentage of immune children in the several localities and indicated whether yellow fever had been present in recent years. This valuable method cannot be used on a scale large enough to permit the detailed mapping of the endemic areas needed for a true appreciation of the distribution of yellow fever or as a guide for control measures. The discovery by Theiler[3] of the suceptibility of the white mouse to yellow fever when inoculated intracerebrally has given us the animal needed for extensive surveys. He showed that yellow fever in the mouse took the form of an encephalitis, and that the mixture of human immune serum with the virus injected would inhibit or defer the infection. After many passages through mice the virus became highly virulent for these animals, causing death as a rule on the fifth or sixth day after inoculation, and lost its power to kill rhesus monkeys, although it continued to produce fever in these animals, and in these respects it assumed the character of a fixed virus.

In order to adapt the protection test in mice to the needs of the field studies which we have carried out, Sawyer and Lloyd[5] sought to make the test more sensitive and regular. They found that fatal encephalitis could be produced by yellow fever virus when introduced intraperitoneally if, at the same time, a mild irritant was injected intracerebrally to localize the virus. Further, if immune serum in suitable amount was injected into the abdomen with the virus, the animal was protected. The technique now being used in the routine application of this intraperitoneal protection test is as follows: The mice are lightly etherized and are given an intracerebral injection of 0.03 cc. of 2 per cent starch in physiologic sodium chlorid solution. They are then given an intraperitoneal injection of 0.2 cc. of a 20 per cent suspension of brain tissue from infected mice and 0.4 cc. of the serum to be tested. In the control injections normal human serum is given in the place of the unknown serum. A group of 6 mice is used as a unit in the examination of each specimen of blood. The mice in the control groups die as a rule from 5 to 10 days after inoculation, usually after 5 or 6 days. The groups receiving non-immune sera die like the control animals, while those receiving potent immune sera should survive for at least 10 days.

The survey of endemic areas with the help of the protection test in mice is now under way. Sera are being collected under a systematic plan in West Africa, Brazil and elsewhere by our field staff, and are being examined in Lagos, Nigeria, West Africa, in Bahia, Brazil, and in our laboratory in New York. Later we shall know how widespread yellow fever infection really is, and where governments can most intelligently concentrate their control work.

The intraperitoneal protection test in mice may be used also in the titration of immune sera with regard to protective power, and is useful in the study of individual cases of yellow fever. It may help in deciding the diagnosis late in the disease or during convalescence. A laboratory worker recently contracted yellow fever while handling virus from mice, and his case was studied by Berry and Kitchen.[6] They had the coöperation of Dr. Max Theiler, who made tests of the patient's serum by the intraperitoneal method in mice and also injected specimens of blood intracerebrally into mice. The serum of the patient showed no protective power on the second and third days of the disease, but there was distinct, though slight, protection on the fourth day. The specimens obtained on the fifth and sixth days gave definite protection. Mice were infected by the blood specimens drawn on the first, second, and third days of illness, but not by those taken on the fourth or fifth days. Rhesus monkeys were inoculated with blood taken on the first, fourth and fifth days, and all three came down with yellow fever. Thus, with the highly sensitive protection test in mice and the inoculation of the very susceptible *Macacus rhesus* monkeys, it was possible to demonstrate

the presence of active virus and immune bodies against that virus in the same specimens of blood—those taken on the fourth and fifth days. The diagnosis of yellow fever was proved by each of the three procedures mentioned, as the serum had been tested shortly before the illness and found to be devoid of antibodies protective against yellow fever.

**Summary.** 1. Yellow fever still persists in South America, and is widely prevalent in West Africa.

2. In the endemic areas cases are few and apparently sporadic, but the virus when carried outside such areas gives rise to true epidemics.

3. The immunity following an attack is solid and permanent.

4. The protection test in monkeys or in mice will show the presence or absence of immunity.

5. The boundaries of an endemic area may be drawn by examining the blood serum of children, and determining whether or not any of them are immune and so establishing the presence of yellow fever in the area within the life time of the children.

6. The test with mice is more delicate than that with monkeys and may be used to titrate immune sera after an attack or after vaccination.

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## THE PRESENCE OF HETEROPHILE ANTIBODIES IN INFECTIOUS MONONUCLEOSIS.*

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The term *heterophile antibody* applies to antibodies having the capacity to react with certain antigens, which are quite different from, and phylogenetically unrelated to the one instrumental in

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producing the antibody response. Their existence became recognized largely through the work of Forssman in 1911,[1] whose name has been attached to antigens capable of eliciting the heterophile response. Since their discovery they have been studied experimentally by many investigators, to which Davidsohn's exhaustive review[2] bears testimomy, but only recently have the principles involved found clinical application. No attempt will be made in this paper to review the development of knowledge of heterophile antigens and antibodies, for the subject is a complex one, probably still in its infancy, and furthermore the reader may be referred to Davidsohn's review,[2] and recent textbook articles by Bull,[3] and Topley and Wilson.[4] However, a few definitive statements relative to the nature of the phenomena involved may be warranted.

Briefly it has been shown that certain substances such as emulsions of cells obtained from the organs of the guinea pig, cat, dog and horse, a number of other mammals, birds and certain fish, when injected into an appropriate animal such as the rabbit, are capable of giving rise to, not only specific antibodies, but also nonspecific antibodies which are demonstrable in varying degree in the form of hemolysins and agglutinins for sheep cells. Chemically, the antigen capable of eliciting this response has been defined as lipoid-protein complex. The whole complex is necessary for the production of heterophile antibodies, whereas the lipoid fraction, which can be extracted with alcohol, reacts with antisera *in vitro*, but is incapable of producing heterophile antibodies. In other words, the antigenic capacity depends on the integrity of the lipoid-protein complex and the extracted lipoid affords another example of a haptene. Apparently the substances which contain the heterophile or Forssman antigen are widespread throughout the animal kingdom, representing a growing list, often referred to as the so-called *guinea pig* group of substances. In contrast, stands the so-called *rabbit group*, representing substances in which the Forssman antigen has not been found, such as the organs of the rabbit, man, ox, rat, etc.

Only a few pathogenic bacteria are known to belong to the guinea pig group and probably for this reason heterophile antibodies have not been demonstrated in appreciable amounts among patients suffering from disease induced by most bacterial agents. Nevertheless, the phenomenon of heterophile antibody production may occur in human beings into whom substances containing the heterophile antigen have been injected. This has been shown by Davidsohn,[5, 6] who has demonstrated the enhanced presence of lysins and agglutinins for sheep cells in the serum of patients who had been injected with horse serum. As a corollary to this finding Davidsohn also made the important observation that the average titers for agglutinins and hemolysins were very much higher among patients who had been injected with horse serum and who subsequently developed

serum disease, than among those who did not develop allergic symptoms. In cases of serum disease produced by the injection of *bovine* serum, heterophile antibodies were not found.

Following the publication of Davidsohn's observations on the presence of heterophile antibodies in serum disease, it seemed to us that a study of this type could be directed against a number of clinical conditions in which heterophile antibodies might exist. Our attention was first turned to cases of rheumatic fever, owing to the resemblance which many of the symptoms of this disease, such as skin eruptions, glandular enlargement and polyarthritis bear to serum disease; but we were unable to demonstrate a consistent or an appreciable increase in the heterophile antibody content of the sera from patients suffering from this condition. In the course of this study a number of controls from individuals suffering from serum disease and a variety of other clinical conditions were assembled. Quite by accident it was discovered that heterophile antibodies (demonstrable in the form of sheep cell agglutinins) were present in a specimen of serum from a patient, ill with infectious mononucleosis, in much higher concentration than has been described in serum disease or in any other clinical condition which we have studied. Subsequently we have confirmed this finding in the acute phases of 3 other cases of infectious mononucleosis and our observations upon this disease furnish the basis of this report.

**Methods.** We have employed the methods used by Davidsohn for determining the presence and titer of sheep cell agglutinins and hemolysins.[5] The technique is quite simple.

*Sheep Cell Agglutinins.* Sera, obtained as for a Wassermann test, were inactivated for 15 minutes at 55° C.* Dilutions of inactivated sera, ranging from 1 to 4 to 1 to 32 (or higher if the heterophile antibody content was suspected to be present in unusual concentration), were set up in 0.5 cc. portions. To these 0.5 cc. of a 2 per cent suspension of sheep cells† were added, followed by 1 cc. of salt solution, thus bringing the total volume in each tube to 2 cc. The test tubes were shaken and placed in the water bath at 38° C. for 1 hour, left in the icebox overnight and on the following morning were read, after each tube had been inverted three times with its mouth covered by the finger tip. A series of tubes which had been recently inverted and then allowed to settle for a few minutes is shown in Fig. 1. The titer of sheep cell agglutinins in this instance was 1 to 128.

For the sake of conformity with previous work, the readings have been recorded in terms of the original dilution of the 0.5 cc. of sera added to each tube. With the subsequent addition of 0.5 cc. of the suspension of sheep cells and 1 cc. of saline, the dilution of serum becomes much higher so that actually the tube designated 1 to 4 contains 0.12 cc. of serum in

* Experiments were performed upon the optimum time of inactivation, which proved to be between 15 and 30 minutes. Samples of sera inactivated for longer periods of time seemed to show diminution of heterophile antibody content.

† The sheep cells, which were obtained fresh each week, had been washed three times in saline and were allowed to stand in saline in the icebox for a period of 2 to 5 days before using. We are indebted to Dr. G. H. Smith and Mrs. Edna Lyons, of the Department of Immunology, Yale University for supplying us with washed sheep cells during the course of this work.

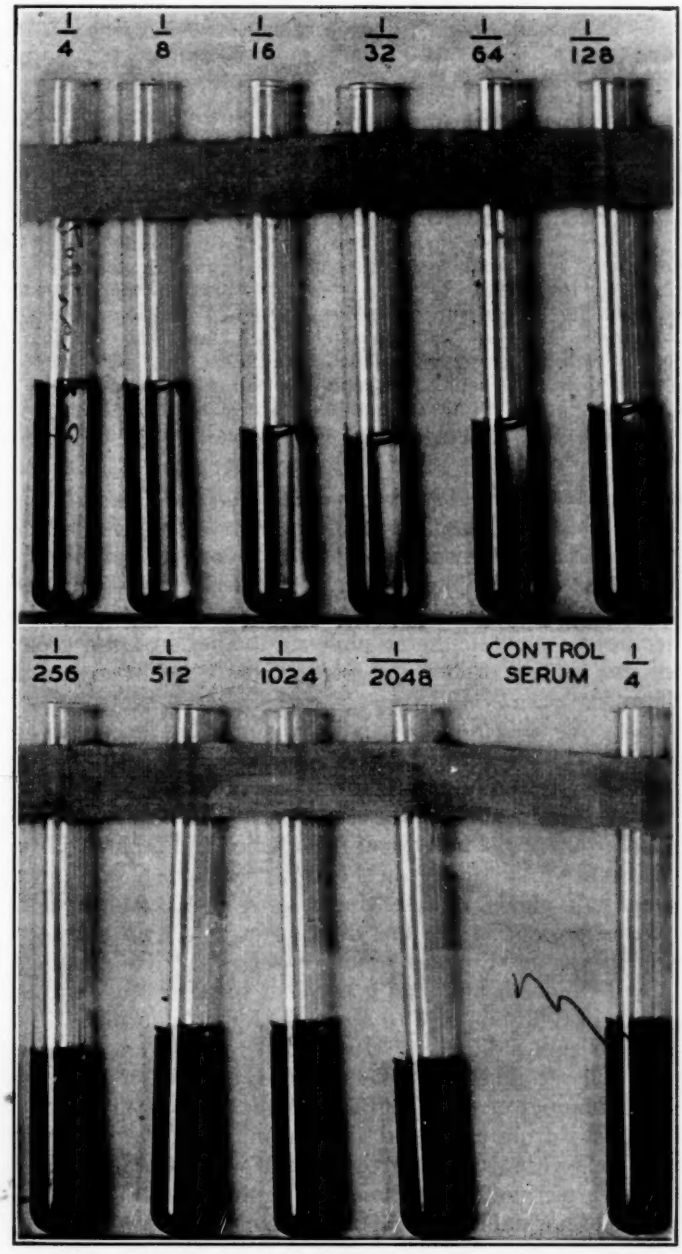


FIG. 1.—Sheep cell agglutinin determination. A series of tubes containing sheep cells and dilutions of serum, from a patient with infectious mononucleosis. The titer is 1 to 128. A normal control serum (dilution, 1 to 4) is shown on the right.

2 cc. of cell suspension; that designated 1 to 8 contains 0.06 cc. of serum, in 2 cc. of suspension. Legends for recording the readings are given in the following terms:

+++ firm disk.
++ disk easily broken into large flakes.
+ fine agglutination.
± barely perceptible, but definite agglutination.

*Sheep Cell Hemolysins.* In the observations recorded below all of the results have been given in terms of sheep cell agglutinins. Sheep cell hemolysins were found to parallel the agglutinin content with such regularity that the former have not been recorded. In many of our earlier determinations both tests were run and were found to serve as a rough check, one for the other.

Hemolysin tests were run as follows: Original dilutions of 0.5 cc. of inactivated sera, similar to those used in the agglutinin tests, were employed. To these 1 cc. of guinea pig complement in a dilution of 1 to 30 was added, then 0.5 cc. of a 2 per cent suspension of sheep cells, followed by 1 cc. of saline, thus bringing the total volume to 3 cc. in each tube. The tubes were shaken, placed for 1 hour in a water bath at 38° C. and read.

**Results.** *Sheep Cell Agglutinins in Normal and General Hospital Patients.* Before attempting to interpret our findings in different clinical conditions, it seemed important to assemble a large group of control cases, including as many normal individuals as possible, in order to obtain a base line for subsequent studies. Similar work on the measurement of heterophile antibodies in large groups of normal individuals or hospital patients may be briefly reviewed as follows:

The presence of hemolysins and agglutinins for sheep cells in low dilutions of supposedly normal human sera has been repeatedly observed.[5, 6, 7, 8] Some investigators[9] also give figures to show that their occurrence in human beings may be influenced somewhat by the blood group of the individual from which the serum is obtained. In Davidsohn's first studies[5] on the presence of sheep cell agglutinins in normal individuals, representing a series of 450 adults, he found them to be present in the low dilution of 1 to 4 in 4.2 per cent. Subsequently,[6] in studying a larger series (which included 850 adults and children) he found 9 per cent to possess agglutinins for sheep cells in dilutions of 1 to 4, only a few in dilutions of 1 to 8; and none in higher dilutions. He believed the higher percentages, present in the second series, which included children, to be due to the increasing number of therapeutic immunizations with various sera administered during childhood. Agglutinins for the blood cells of other animals were studied by this author who records the presence of ox, guinea pig and rabbit blood cell agglutinins in a much higher percentage of normal individuals, thus placing sheep cells in a rather unique position from the standpoint of their reactions with human sera.

A more extensive study on the incidence of *nonspecific* agglutinins in man is that of Friedberger and his coworkers.[10] These

investigators have determined the presence and concentration of sheep cell hemolysins and rabbit cell agglutinins in individuals of different age groups, finding that both sets of antibodies were absent at birth, that they were demonstrable in low concentrations among 20 per cent of infants during the first year of life; 60 per cent by the fifth year, and 90 per cent by the tenth. This high incidence remained throughout adolescence and early adult life, but subsequently fell slowly to about 20 per cent in old age. In interpreting these findings the German investigators have raised the question as to whether defensive antibodies may not be formed in growing children as an expression of *immunologic maturation*.

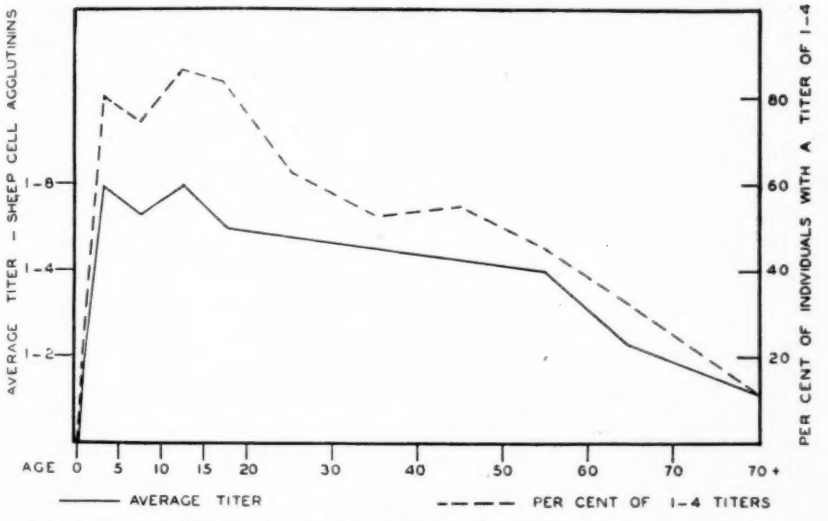


FIG. 2.—The age distribution of sheep cell agglutinins in sera from a series of 275 general hospital patients.

Our own control studies on the presence of sheep cell agglutinins in human sera have been made with particular reference to their concentration in different sets of clinical conditions. We have not succeeded in assembling a very large series of normal controls, but in our series of 275 general hospital patients there were many individuals in whom there was no reason to suspect an infection or any deviation from the normal antibody content of their sera. An accurate history in each individual with regard to the injection of horse serum for therapeutic or prophylactic purposes was not obtained. However, in none of the 275 control patients, included in this series, were sheep cell agglutinins found in unusually high concentration. We attempted to secure a wide age distribution in this group by including placental blood, infants under 1 and 5 years, and adequate groups of individuals representing different decades

of life up to the age of 70. The results are shown in Fig. 2. Here it will be seen that in none of the 10 samples of placental or cord blood were sheep cell agglutinins present. There is a rapid rise during the first 5 years of life reaching an irregular peak between 5 and 15, at which time the average concentration is close to 1 to 8; it then undergoes a gradual decline. If expressed in terms of the percentage of individuals in whom sheep cell agglutinins were demonstrable in a concentration of 1 to 4 it will be seen that there is a sharp rise from zero at birth to 80 per cent by the fifth year, and 86 per cent by the fifteenth year. It then declines to 60 per cent by the thirtieth year; 54 per cent by the fortieth; and 40 per cent by the sixtieth year, etc. Our findings show the relative frequency with which low concentrations of sheep cell agglutinins are usually found in human sera, and furnish a rough base line on which deviations from the average curve may be ascertained. They are essentially in agreement with those of Friedberger *et al.*,[10] who in a similar manner have studied the age distribution of sheep cell hemolysins and rabbit cell agglutinins in a group of hospital patients.

*Sheep Cell Agglutinins in Various Clinical Conditions.* In Table 1 are shown some of the clinical conditions in which our determinations of sheep cell agglutinins have been made. In Group II, which includes a number of different examples of infectious disease, there seems to be a slight tendency for maximum titers to run above the usual figures (Fig. 2), although only in a single instance was a titer of 1 to 32 recorded. Seven cases of serum disease are shown in Group IV, in which a very appreciable increase of the agglutinin titer was found in 90 per cent of the cases. In Group V are recorded the findings in the 4 cases of infectious mononucleosis which we had the opportunity of studying. In all of them titers are recorded which are higher than those observed in our most severe cases of serum disease, in one instance representing an original dilution of 1 to 1024.* A number of examples of other blood dyscrasias have been assembled in Group VI, including 2 cases of chronic lymphatic leukemia. In none of these, however, was an increase in the sheep cell agglutinins observed, except in a single case which will be discussed more in detail later. These findings show that the presence of a high concentration of heterophile antibodies is a fairly consistent feature of infectious mononucleosis, and that apart from the cases of serum disease, appreciable amounts of heterophile antibodies have not appeared in our controls, except in one notable case.

*The Relationship of Sheep Cell Agglutinins to the Symptomatology of Infectious Mononucleosis.* Brief clinical details of 2 of our 4 cases are given in the following case reports. The temperature

* Absorption determinations were run in one of our cases of infectious mononucleosis. It was shown that the agglutinins could be absorbed by sheep cells.

TABLE 1.—SHEEP CELL AGGLUTININS IN MISCELLANEOUS CONDITIONS, SERUM DISEASE AND INFECTIOUS MONONUCLEOSIS

| Group. | Type of case or diagnosis. | No. of cases. | | Dilutions of patient's serum. | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | 1/8 | 1/16 | 1/32 | 1/64 | 1/128 | 1/256 | 1/512 | 1/1024 |
| I. | Normal | 11 | Maximum | ± | − | − | − | − | − | − | − |
| | | | Minimum | − | − | − | − | − | − | − | − |
| II. Infections | Tuberculosis | 15 | Maximum | ++ | + | − | − | − | − | − | − |
| | | | Minimum | − | − | − | − | − | − | − | − |
| | Syphilis | 6 | Maximum | + | − | − | − | − | − | − | − |
| | | | Minimum | − | − | − | − | − | − | − | − |
| | Rheumatic fever and rheumatoid arthritis | 12 | Maximum | ++ | + | ± | − | − | − | − | − |
| | | | Minimum | − | − | − | − | − | − | − | − |
| | Streptococcus infections | 13 | Maximum | + | + | − | − | − | − | − | − |
| | | | Minimum | − | − | − | − | − | − | − | − |
| | Vincent's infections | 2 | Maximum | ± | − | − | − | − | − | − | − |
| | | | Minimum | − | − | − | − | − | − | − | − |
| | Lung abscess | 1 | .... | − | − | − | − | − | − | − | − |
| | Miscellaneous infections | 11 | Maximum | + | − | − | − | − | − | − | − |
| | | | Minimum | − | − | − | − | − | − | − | − |
| III. | Bronchial asthma | 4 | Maximum | ++ | + | − | − | − | − | − | − |
| | | | Minimum | − | − | − | − | − | − | − | − |
| | Miscellaneous conditions | 11 | Maximum | ++ | + | − | − | − | − | − | − |
| | | | Minimum | − | − | − | − | − | − | − | − |
| IV. Serum disease | Severe serum disease | 3 | Maximum | +++ | +++ | +++ | ++ | − | − | − | − |
| | | | Minimum | ++ | ++ | + | ± | − | − | − | − |
| | Mild serum disease | 4 | Maximum | +++ | +++ | ++ | ++ | − | − | − | − |
| | | | Minimum | ± | − | − | − | − | − | − | − |
| V. Infectious mononucleosis | Early | 1* | .... | +++ | +++ | +++ | ++ | + | − | − | − |
| | Height | 4* | Maximum | +++ | +++ | +++ | +++ | +++ | ++ | ++ | ± |
| | | | Minimum | +++ | +++ | +++ | ++ | + | − | − | − |
| | Late | 3* | Maximum | +++ | +++ | +++ | +++ | ++ | ± | − | − |
| | | | Minimum | +++ | +++ | ++ | ++ | − | − | − | − |
| VI. Other blood dyscrasias | Pernicious anemia | 4 | Maximum | ++ | − | − | − | − | − | − | − |
| | | | Minimum | − | − | − | − | − | − | − | − |
| | Purpura hemorrhagica | 2 | .... | − | − | − | − | − | − | − | − |
| | Lymphatic leukemia | 2 | .... | − | − | − | − | − | − | − | − |
| | Myelogenous leukemia | 2 | Maximum | + | − | − | − | − | − | − | − |
| | | | Minimum | − | − | − | − | − | − | − | − |
| | Hodgkin's disease | 1 | .... | − | − | − | − | − | − | − | − |
| | Aplastic anemia (?) | 1 | .... | +++ | +++ | ++ | ++ | + | − | − | − |

* Representing a total of 4 cases.

curves, blood counts, and heterophile antibody titers are also shown in Figs. 3 and 4.

**Case Reports.** CASE 1.—Fe, a white, male, medical student, aged 22 years, was admitted to the New Haven Hospital on February 7, 1930,

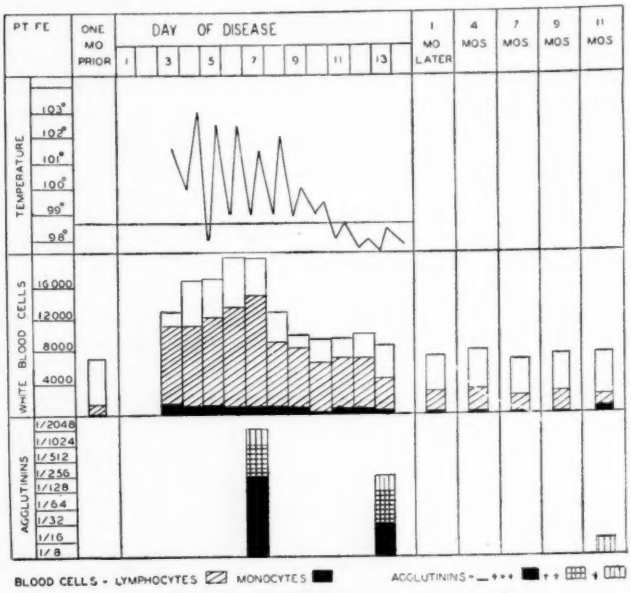


FIG. 3.—Case 1. Infectious mononucleosis.

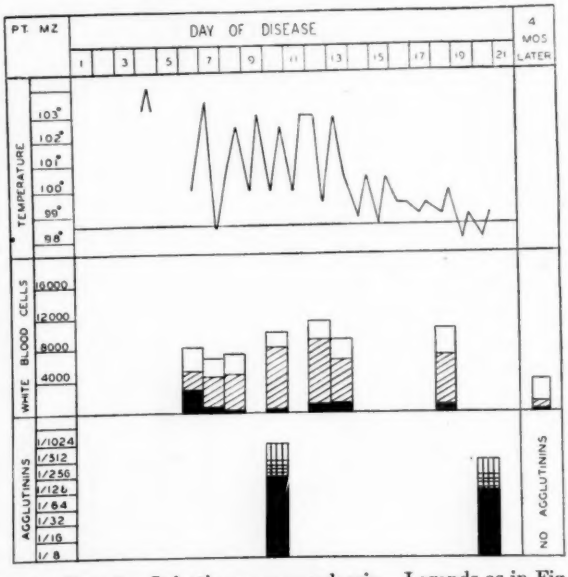


FIG. 4.—Case 2. Infectious mononucleosis. Legends as in Fig. 3.

complaining of malaise, headache, fever and swollen and tender glands. He was a member of the class in clinical microscopy and as such had performed a number of leukocyte and differential counts upon himself 1 month prior to the onset of his illness. Fortunately we had preserved one of these smears which showed a normal differential count.

For a period of 10 days prior to the development of acute symptoms he had been feeling below par. Three days before admission he felt weak and noticed that the glands in his neck and axilla were swollen. Apparently he had not suffered from sore throat.

On admission his temperature was found to be 100° F. The throat was red, but there were no lesions in the oral cavity. There was marked enlargement of cervical lymph glands and slight redness of the overlying skin; the axillary and inguinal lymph glands were also enlarged. The total white blood cell count was 12,800, of which 75 per cent were lymphoid cells, and 13 per cent were monocytes. A throat culture showed an essentially normal flora. The blood culture was negative. On the day after admission he complained of chilly sensations, some photophobia, and hyperesthesia over the skin of the neck. Four days later the temperature began to fall and the lymph glands to recede in size. His course and subsequent blood counts are shown in Fig. 3.

On the seventh day of his illness sheep cell agglutinins were found in this patient's blood to the unusually high dilution of 1 to 1024; on the thirteenth day they were present in a dilution of 1 to 128. The presence of other agglutinins was also investigated in samples of serum obtained on the seventh and thirteenth days of his disease. Tests were made against Bacillus typhosus, Bacillus paratyphosus A and B, Bacillus proteus X-19 and Brucella abortus. Agglutinins were not demonstrated for any of these organisms in dilutions of 1 to 20 or higher.

After his discharge from the hospital, blood counts were obtained at intervals of 2 to 4 months. A slight increase in monocytes was noted in three of these counts. Sheep cell agglutinins, when tested 11 months after his illness, were found to be within normal limits.

The interesting feature of this case was the extraordinary high titer to which sheep cell agglutinins were demonstrated during the early stages of a relatively short, febrile illness, together with the fact that the titer had begun to fall with the subsidence of symptoms. The blood count continued to show a slight increase of monocytes almost a year after his illness, but at this time sheep cell agglutinins had fallen to within normal limits.

Details of another case appear below, and are also shown in Fig. 4.

CASE 2.—Mz, a white, female, medical student, aged 21 years, was admitted to the New Haven Hospital on October 25, 1930, complaining of fever.

She gave a previous history of having had frequent attacks of tonsillitis. A week prior to admission she had had a slight sore throat; 2 days later her temperature had been 101° F., and later 104° F.

On admission the patient was slightly jaundiced; there was diffuse redness of the pharynx and generalized glandular enlargement. The liver and spleen were easily palpable. The total white blood cell count was 8000 per c.mm., with 65 per cent lymphoid cells and 12 per cent monocytes. The throat culture showed many hemolytic streptococci; an occasional spirillum and fusiform bacillus was seen in the stained smear. Her subsequent course is shown in Fig. 4.

The jaundice became more intense, and on the tenth day of her disease, the icteric index was 36; the van den Bergh gave a positive indirect reaction, quantitatively equivalent to 6.25 mg. of bilirubin per 100 cc. of blood.

A liver function test, performed by the injection of bromsulphalein at this time, showed the presence of 55 per cent of the dye in the serum 5 minutes after injection and 20 per cent 30 minutes after injection.

After running a febrile course, which in all lasted about 15 days, there was a rapid subsidence of symptoms, with diminution in the size of the glands. The mononucleosis was still marked on the eighteenth day of the disease. Four months later the blood findings were essentially normal except that monocytes numbered 8 per cent.

At the height of her illness sheep cell agglutinins were present in a titer of 1 to 512; during early convalescence the titer was 1 to 256. Four months later agglutinins were absent.

*Sheep Cell Agglutinins in Conditions Other than Serum Disease and Infectious Mononucleosis.* In one of Davidsohn's articles the authors call attention to the fact that a high titer of sheep cell agglutinins may rarely occur in certain pathologic conditions other than those in which horse serum has been injected, recording a single instance of a patient receiving insulin injections, in whom a titer of 1 to 64 was observed.[11] Among the many examples of different pathologic conditions which we have studied, a titer above 1 to 32 was not observed, except in our cases of serum disease and infectious mononucleosis. There was, however, one notable exception which was an obscure case terminating fatally. Clinical details of this case are shown briefly in Fig. 5 and in the following case report:

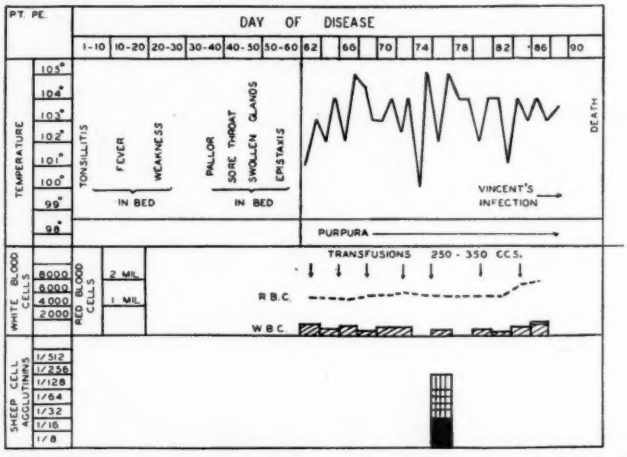


FIG. 5.—An obscure case terminating fatally in which sheep-cell agglutinins were found shortly before death in a titer of 1 to 128. Legends as in Fig. 3.

Case 3.—Pe, an Italian female, aged 19 years, was admitted to the New Haven Hospital on October 16, 1930, complaining of fever, sore throat and weakness. She had apparently been suffering from these symptoms for a period of 2 months. On examination there was marked pallor and some emaciation. The tonsils were enlarged as were also some of the regional, cervical lymph glands, but this was not pronounced. The spleen

was palpable. An eye ground examination revealed retinal hemorrhages, although bleeding was not particularly prominent elsewhere. Blood cultures were consistently negative.

The initial examination of the blood showed 1,200,000 red cells and 1200 white cells, with an absence of polymorphonuclears. The platelets numbered 75,000 and 80,000 on two examinations. Subsequent blood findings are recorded in Fig. 5.

The patient's course was steadily downhill. Two weeks after admission she developed an ulcerative lesion on the right tonsil from which Vincent's spirilla and fusiform bacilli were demonstrated. On the eighty-ninth day of her disease she was discharged from the hospital against advice and died at home a few days later. A satisfactory diagnosis of this case was not reached. In many respects the white blood cell picture recalled that of agranulocytic angina, although the severe anemia spoke against this, and the case has been listed by us as either an example of *aleukemic leukemia* or *aplastic anemia*.

A single determination of the agglutinins for sheep cells was made on the seventy-fifth day of her disease. They were found in a serum dilution of 1 to 128. Prior to this determination she had received a number of blood transfusions (Fig. 5). We do not know what effect this may have had upon the heterophile antibody content of her serum. The patient was Group B, and the cells of this group do not contain the heterophile antigen.[12]

*Observations on the Relation of Vincent's Infection to Infectious Mononucleosis.* Although the causative agent of infectious mononucleosis is unknown, many bacteria have been incriminated, notably members of the streptococcus group, diphtheroid bacilli, and Vincent's organisms. The association with bacteria thought to cause lesions in the mouth and throat is strong owing to the frequent presence of tonsillitis and oral lesions as an initial symptom of the disease. Recently, however, several observers have raised the question as to whether the disease may not be due to a vibrio. Nyfeldt[13] has reported the isolation of such an organism from the blood of a patient ill with infectious mononucleosis. Gorham, Smith, and Hunt[14] have also assembled evidence, through the inoculation of guinea pigs, to show that a vibrio may be of etiologic import.

We have not gathered data which have bearing upon questions of the etiology of infectious mononucleosis, except perhaps a few observations which concern the relationship of Vincent's organisms to this disease. This possible relationship has been approached from three angles: (*a*) The incidence of Vincent's organism in the throats of our small series of patients; (*b*) an estimation of heterophile antibodies in serum from control cases of Vincent's angina; (*c*) tests to establish whether or not Vincent's fusiform bacilli contain the heterophile antigen.

(*a*) *The Incidence of Vincent's Organisms.* From 3 of our 4 cases of infectious mononucleosis, Vincent's organisms were obtained, as follows: Patient 4 (Pn) had an ulcerated lesion on the tonsil from which spirilla and fusiform bacilli could be demonstrated in large numbers. The throat flora of this patient was otherwise not

remarkable. In Patients 2 (Mz), and 3 (Bd), Vincent's organisms were demonstrated in smears from the gums but not in large numbers. In both of these patients the tonsils were inflamed and appreciable numbers of hemolytic streptococci were present in the throat cultures. In Patient 1 (Fe), Vincent's organisms were not found; there were no appreciable tonsillar lesions, and the throat flora failed to show any abnormalities.

(*b*) *The Determination of Heterophile Antibodies in Vincent's Angina.* Two cases suffering from ulcerative lesions of the mouth, from which large numbers of spirilla and fusiform bacilli could be demonstrated, are included among our series of controls in Table 1. In neither of them were sheep cell agglutinins demonstrable in the serum. It follows, therefore, that if one assumes that Vincent's organisms are in any way responsible for the disease known as infectious mononucleosis, one must also assume that a far more extensive antibody response is elicited in this disease than is seen in the usual case of Vincent's angina.

(*c*) *Tests to Determine Whether or not Vincent's Fusiform Bacilli Contain the Heterophile Antigen.* Two rabbits were inoculated with suspensions of living organisms from a stock strain of fusiform bacilli.* In both rabbits specific agglutinins for the strain of fusiform bacillus employed as an antigen were rapidly developed in high titers. In neither antisera were heterophile antibodies (demonstrable as agglutinins for sheep cells) detected at any time during the process of immunization. It is, perhaps, unfortunate that we did not use a strain which had been isolated from one of our cases of infectious mononucleosis, and also that suspension of spirilla were not tried for the immunization experiments, but the difficulty of growing these organisms precluded the determination of these points.

Certain complexities arise in the interpretation of this experiment largely because of our limited knowledge of the properties of Vincent's organisms, for the relationship between the spirilla and fusiform bacilli is not clear. However, it has seemed somewhat pertinent to us that the particular strain of fusiform bacilli which we did test, proved to be one which failed to elicit the slightest degree of heterophile antibody response.

**Discussion.** Our findings indicate that sheep cells agglutinins and hemolysins appear in surprisingly high concentrations in the serum of patients during the acute stages of infectious mononucleosis. It is difficult to conceive of this phenomenon other than as an example of heterophile antibody production, perhaps analogous to the response which is known to exist in the acute phases of serum disease as a result of the injection of horse serum. Although the

* We are indebted to Mr. L. W. Slanetz, of the Department of Bacteriology, Yale University, for these cultures. The strain had been isolated from the gums of a patient several months previously and had been grown anaërobically during this time.

mechanisms involved are not clear, it is unlikely that the disease known as infectious mononucleosis should be the only condition in which this response is elicited without the *artificial* introduction into the body of a substance containing the heterophile antigen. Indeed, one exceptional case, which we have already reported above, would suggest that it may occasionally be demonstrated in other conditions. Nevertheless, in spite of the fact that the limits of the reaction which we have described have not been tested, it would seem to be of some diagnostic value. In a sense, however, it appears to be of more theoretical than practical interest. Theoretical interest centers about the fact that heterophile antibodies may be produced or enhanced during the course of human infectious disease, and in one disease in particular, in which the etiology has not been established. Furthermore, that two clinical entities with widely differing symptomatology, such as serum disease and infectious mononucleosis, would elicit the same type of serologic response is also worthy of interest. In serum disease the phenomenon of heterophile antibody production would seem to be more or less explainable, but in infectious mononucleosis we have no rational explanation. A possible one would be that these antibodies are produced as part of the direct immunologic response to infection by the unknown agent producing the disease. This theory will be difficult to prove, however, until the unknown infective agent is isolated and tested for the presence of the heterophile antigen. In the light of this approach, however, we have been unable to secure evidence that Vincent's fusiform bacilli are of etiologic import in this disease. On the other hand, it is also conceivable that the phenomenon which we have described is in the nature of an isoagglutinin response to the presence of an excess of *abnormal* cells either present in the blood or elsewhere. In any event, however, further work on this problem should logically be concentrated upon a search for the carrier of the heterophile antigen which probably lurks somewhere in the human body during the active stages of this disease.

**Conclusions.** 1. Heterophile antibodies, demonstrable in the form of sheep cell agglutinins, have been recorded in rather high concentrations in the active stages of 4 cases of infectious mononucleosis.

2. Apart from cases of serum disease, and one notable exception, we have failed to note this finding in a large series of cases representing a variety of clinical conditions, including cases of Vincent's angina, lymphatic leukemia and other blood dyscrasias.

3. There would seem to be two possible explanations for this finding: (1) that the unknown agent responsible for infectious mononucleosis contains the heterophile antigen; (2) that we are dealing with an example of isoagglutinin production elicited by abnormal cells, which are present either in the blood, or elsewhere, during active stages of the disease.

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## MYELOID CELL HYPERPLASIA OF THE BONE MARROW IN AGRANULYOCYTIC ANGINA.

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The current concept of the bone marrow changes in so-called agranulocytic angina is that there exists, at least terminally, a more or less complete absence[1] of white cells of the granular (myeloid) series. This "granulocytic aplasia" concept has developed partly

on the basis of bone marrow studies indicating an apparently selective disappearance of the granular leukocytes and their progenitors and partly on the basis of analogy to established findings in certain other conditions, such as benzol poisoning, with its "selective" attack on formative tissues of the granular cells and blood platelets.

The possibility that such a concept may not be entirely well founded in fact, and may be misleading in implication, has come to mind from personal study of the bone marrow of 3 recent fatal cases. In 1 of these, reported below, the marrow of most of the bones examined contained "actively hemopoietic areas" filled with myelocytes, promyelocytes and myeloblasts, while the peripheral blood contained only 200 white blood cells per c.mm. (all lymphocytes). Similar, although less obvious, absence of myeloid white cell aplasia was found in the marrow of the other 2 cases. One of these died after months of illness characterized by repeated severe relapses and incomplete remissions. This patient's marrow, in most of the bones, was more nearly aplastic as regards granular series cells than any other marrow of such cases personally examined; but even this one showed numerous myeloblasts and a few myelocytes in the rib marrow, whereas her terminal white blood count was only 500 cells per c.mm. (all lymphocytes).

Necropsy was performed in these cases within 2 hours of death, and fresh bone marrow, spleen and lymph node smears were stained at once by the usual hematologic methods (Wright's, oxidase and cresyl blue). We believe this fresh smear technique to be a valuable hematologic adjunct to the study of the routine marrow sections of the pathologist.

While the majority opinion and findings of those who have reported on this disease would seem to favor the "aplastic" marrow hypothesis, there are several reports of myeloblastic and myelocytic hyperplasia on record,[2] to which the following is added:

**Case Report.** Mrs. L. S., a widow, aged 58 years, white, a native of Pennsylvania, was admitted to the care of Dr. F. C. Wood, University of Pennsylvania Hospital, on May 17, 1931. She had been well, except for occasional "neuritis" in her right arm and occasional sore throats, until May 15, when, following exposure to inclement weather, she developed increasing sore throat, fever and vomiting. Dr. Wood saw her on the morning of May 17 and made a leukocyte count which showed "less than 1000 leukocytes" per c.mm. and confirmed his clinical suspicion of "agranulocytic angina." Her past medical history included quinsy in childhood and several attacks of sore throat and vomiting in the past 2 years which seemed to her just like the present attack. In addition she had suffered from chronic discharging otitis media for some years, frequent headaches, acne and chronic constipation. She had "malaria" in adolescence and transient glycosuria (1911 to 1913). Intermittently for about 20 years the patient had noted recurring purpuric spots on her body, but had suffered no other hemorrhages. This purpura ceased spontaneously in 1925 and did not recur. There was no suggestion of hay fever, asthma, hives or drug idiosyncrasy obtainable in her past history.

The *family history* was interesting in that of 7 children born to the patient 3 had died in early infancy and 1 of these had purpuric blotches on the skin. Her parents died in old age and 4 siblings and 2 full-grown children were reported as living and well. One sister died of pulmonary tuberculosis.

*Physical Findings.* On admission to the hospital, examination showed high fever (104° F.), slight jaundice and the rather characteristic multiple ulcerations in the nasopharynx and tonsillar regions, each ulcer being covered by patchy grayish exudate and surrounded by a very thin zone of slight inflammatory reaction. There was slight general pharyngeal edema. The gums (edentulous) and tongue showed no ulceration. There was little or no cervical or other adenopathy. Spleen and liver were not palpably enlarged. Heart, lungs, abdominal organs, blood pressure, reflexes, etc., were all "normal." No petechiæ, no peripheral edema and no vaginal or anal ulcerations were observed.

*Laboratory Data.* "Blood count (May 18, 1931): Red blood cells, 4,800,000 per c.mm.; leukocytes, 350; hemoglobin, 14 gms. (90 per cent.) Differential: 100 per cent lymphocytes. Red cells and platelets appear normal. Platelet count, 265,000 per c.mm. Bleeding and coagulation time tests, normal. Reticulocytes, 0.7 per cent."

May 18: Van den Bergh test: Direct, delayed; indirect, 1.2 units. Icterus index, 20.

May 18: Throat smear and culture: No Vincent's organisms found in the smear. Culture showed predominance of Streptococcus viridans and many hemolytic Staphylococcus aureus organisms.

May 18: Culture from right ear showed predominance of Bacillus pyocyaneus, moderate number of nonhemolytic Staphylococcus albus and many hemolytic streptococci.

May 18: Blood culture, subsequently reported "no growth after 10 days."

May 18: Urinalysis: Acid, 1025; light cloud of albumin, no sugar, many hyalin and light granular casts, a few leukocytes (?).

May 19: White blood count, 440 per c.mm. (all lymphocytes).

May 20: Blood count four hours before death: Red blood cells, 4,300,000 per c.mm.; white cells, 200; hemoglobin, 15.3 gms. (98 per cent.) Wright's stain and oxidase stain showed nothing but an occasional lymphocyte in many fields. Red cells and platelets normal.

*Course and Treatment.* Irregular fever continued, from 100° to 105° F.; tachycardia and dyspnea increased with mucus accumulation in the throat and trachea, dysphagia and terminal delirium. Three blood transfusions were administered and venesection was performed once. Liver extract, calcium gluconate, cod-liver oil, orange juice, oropharyngeal applications, oxygen tent and digitalis completed the list of therapeutic attempts. Roentgen ray therapy was not undertaken because the patient's condition was so grave that removal to the Roentgen ray department seemed inadvisable, especially in view of our experience indicating the fatuity of this form of treatment. The patient died at 3.40 P.M. on May 20, 1931.

*Necropsy Findings.* (Aut. 31-513, two hours after death; significant data as reported by Dr. Klinck.) "Chronic and acute ulcerative follicular tonsillitis." Sections from the tonsils showed "lumina of the crypts filled with necrotic material that is loaded with bacterial growths. The lymphoid cells are extremely plentiful and the bloodvessels congested. A few large mononuclears and a few plasma cells are mixed with the lymphocytes. No polymorphonuclears are present." There was found in some places "much necrosis" and in others "much fibrous tissue." The thyroid gland was normal except for "scattered collections of lymphoid cells" and some "increased interstitial fibrous tissue." The heart showed some "myo-

cardial degeneration; fibrosis of the left ventricle; fatty infiltration of the right ventricle." The lungs showed partial "atelectasis (lower right) and congestion;" the liver, "capsular perivascular sclerosis and congestion;" the spleen, "fibrosis and congestion" (weight, 140 gm.); the pancreas, "fatty atrophy; islet tissue plentiful;" the kidneys, "simple nephrosis;" the adrenals were "negative." The urinary bladder, gastrointestinal tract, aorta, lymph nodes, uterus and other organs all "negative," except the bone marrow, reported grossly as "moderately hyperplastic." The bone marrow sections were referred to Dr. Custer, whose special report is not yet published. However, he tells us that they show a considerable myeloblastic hyperplasia in the femur, tibia, ribs, etc. (Dr. Custer will include this case in a series of marrow studies soon to be published.)

Dr. Klinck made one other observation in this case which may be significant: Lymph nodes seemed scarce and hard to find. Postmortem culture of the splenic pulp was negative. The heart's blood showed a pure culture of Bacillus coli communis. *Pathologist's chief diagnosis:* Agranulocytic angina.

**Study of Fresh Smear Preparations.** Spreads were prepared on coverslips and glass slides from: (1) Blood from capillary pipette puncture of inferior vena cava, (2) heart's blood from right ventricle, (3) rib marrow, (4) sternal marrow, (5) vertebral marrow, (6) femoral marrow, (7) tibial marrow and (8) splenic pulp. These were immediately stained with Wright's and oxidase stain, and in some instances with cresyl blue.

I. Spreads of blood from the inferior vena cava showed red cells well distributed and of normal appearance (except that 1 normoblast was seen). Platelets were plentiful (in large clumps). The white cell count (estimated on the basis of observed ratio of 1 white cell to every 2000 red cells, with the assumption of 5,000,000 red cells per c.mm.) was about 2500 per c.mm. There were obviously more leukocytes in this blood than in that obtained 4 hours before death. Differential count of these cells was 74 per cent lymphocytes, 5 per cent monocytes and 21 per cent indeterminate mononuclear cells, some of which may have been lymphocytes, some possibly monocytes and several apparently young myelocytes (Wright's stain, 100 cells counted). The oxidase stain of the blood showed only 2 per cent granular mononucleated cells (*i. e.*, myelocytes or monocytes) and 98 per cent nongranular (lymphocytes). The cresyl blue preparation showed 2 per cent reticulocytes.

II. Heart's blood spreads were essentially similar to the above except that no oxidase-positive cells were found. One endothelial macrophage was seen which contained remnants of an engulfed cell (lymphocyte?).

III. Rib marrow smears (Wright's) appeared normal in cellular content except for (*a*) the complete absence of polymorphonuclear neutrophils and eosinophils and (*b*) the presence of abnormal numbers of young myelocytes with pale nuclei and many neutrophilic granules in the cytoplasm. Aside from the fat cells, which were present in no excess, the hemopoietic tissue was composed of:

(*a*) Myelocytes and promyelocytes, about 20 per cent. (Fig. 1.) (*b*) Lymphocytes, about 10 per cent. (*c*) Unidentified mononuclear cells of varying sizes (larger than the obvious lymphocytes), with pale nuclei and nongranular or finely granular cytoplasm (either myeloblasts, monocytes or lymphoblasts; probably myeloblasts), about 20 per cent. (*d*) Red blood cells, including numerous normoblasts and a few macronormoblasts, about 50 per cent. (*e*) An occasional typical megakaryocyte. (*f*) A few gigantic cells, each with a large fairly well-defined nucleus (containing nucleoli) and a wide grayish blue finely mottled cytoplasm containing vacuoles and marginal inclusion bodies, which were interpreted as hypertrophied reticulo-endothelial cells. (Figs. 1 and 2.)

Oxidase preparations of the rib marrow showed an essentially similar picture. A differential count of 500 white cells in scattered areas showed 42 per cent granular mononuclear cells (presumably myelocytes) and 58 per cent nongranular cells (lymphocytes, myeloblasts and possibly monocytes). Fifty normoblasts were seen while counting 500 white cells. The gigantic cells previously described from Wright's stain preparation appeared to be nongranular in the oxidase stain.

IV. Sternal and vertebral marrow spreads all showed a less definite picture of myeloid white cell activity, presumably because of osteosclerosis which rendered the smear method unsatisfactory.

V. Femoral marrow spreads were very similar to those of the rib marrow, except for a greater proportion of red cell elements in comparison to white cells. (Fig. 2.)

VI. Tibial marrow smears (from the point selected at necropsy) were entirely fatty.

VII. Splenic pulp smears (Fig. 3) showed nothing but profusion of lymphocytes and lymphoblasts and a few red cells (Wright's stain). These cells were all nongranular in the oxidase preparation.

**Discussion.** The presence of bone marrow progenitors of the granular series of blood cells in this case was not the result of Roentgen ray stimulation[3] because this patient did not receive any such treatment. That these cells were myelocytes and myeloblasts (rather than monocytes) seems evident, although no supravital technique was employed in the staining. Death in this case was due to the disease itself rather than to some intercurrent condition which might be conceived as cutting short the course before the bone marrow lesions had developed to their final stage.[4]

The general leukopenia of this disease involves not only the granulocytes proper but usually the lymphocytes and monocytes as well.[5] The absolute lymphopenia may be considerable even though the relative percentage is greatly increased. Other elements of the blood are rarely affected. The case here described, together with others referred to, make it clear that, at least occasionally, death may occur in uncomplicated "agranulocytic angina" with a

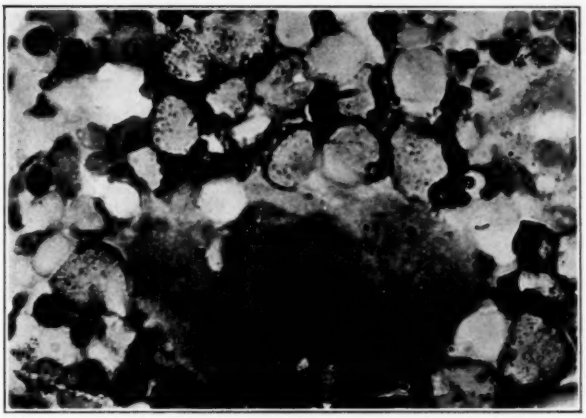

FIG. 1.—Rib marrow (Wright's stain), showing myelocytes, myeloblasts (here appearing very pale), a few lymphocytes, red cells and a large reticuloendothelial cell in the center. (× 644.)

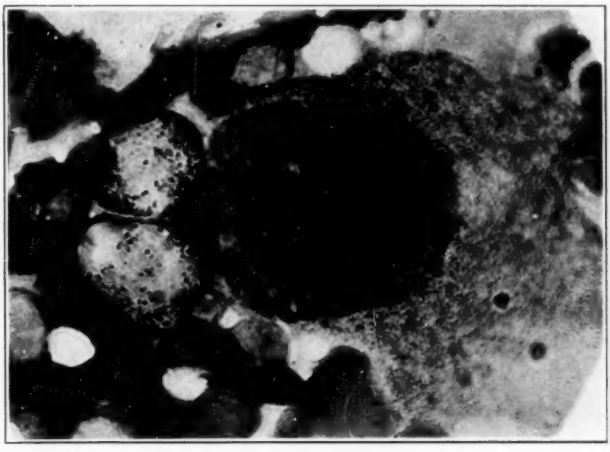

FIG. 2.—Femoral marrow (high magnification), showing a gigantic reticuloendothelial cell, several myelocytes and red cells. (× 1472.)

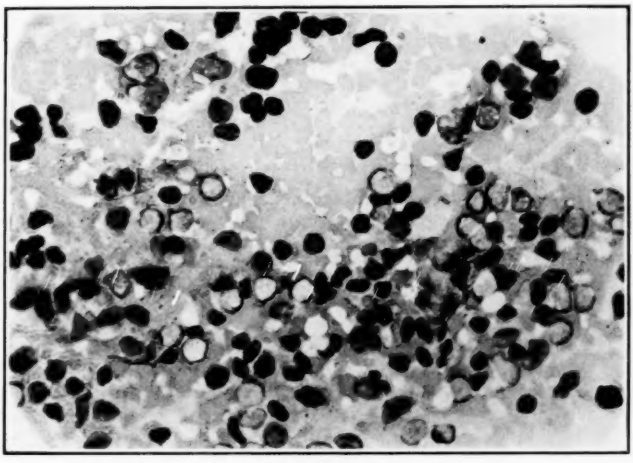

FIG. 3.—Splenic pulp smear (low magnification), showing the small dark lymphocytes; the larger pale, lymphoblasts and monocytes, and red cells (Wright's stain). (× 368.)

profound peripheral leukopenia, while at the same time the leukopoietic centers for granulocytes and lymphocytes (and monocytes?) are well supplied with parent cells. The fact that this state of affairs may exist, even in an occasional case, serves to emphasize the apparent inadequacy of the general "granulocytic aplasia" hypothesis.

It would seem more probable here that a "maturation factor" is at work, either arresting development of white cells in their formative centers or producing degenerative changes in them before sufficient development for normal migration into the bloodstream, or possibly a combination of both factors. This hypothetical factor would conceivably check the granular series of blood cells at the myeloblast-myelocyte stage in the bone marrow and the lymphocyte series at or near the lymphoblast stage in the spleen and lymph nodes. Viewed from this standpoint, the analogies to pernicious anemia are obvious. Pernicious anemia too has remissions and relapses. It too is, as yet, an "idiopathic" disorder with probably a "constitutional" background of prime importance. It too may be closely mimicked by other disorders. Its relapses are characterized by megaloblastic hyperplasia of the bone marrow caused, according to the modern view (Minot), by some maturation-inhibiting factor directed against the red cell series. This concept, transposed to the white cell disturbances of "agranulocytic angina," would in no way deny the probability of a terminal, secondary destruction (or "aplasia") of bone marrow, spleen and lymph node cells in many instances, such as is known to occur in the bone marrow at the end ("aplastic") stage of untreated or poorly treated pernicious anemia.

For these reasons, and with apologies for adding another variant designation to this already much-named disease, the term *pernicious leukopenia* is suggested.

It is, of course, not contended here that anything approximating proof of a maturation factor in the disease has been adduced. The entire problem of the mechanism of leukocytosis and leukopenia in relation to the leukopoietic organs themselves is unsolved. Aleukemic and leukopenic forms and phases of leukemia and intermittent purpura hemorrhagica, as well as pernicious anemia, all present certain interesting analogies to the disease under consideration.

**Summary.** 1. Myelocytes and myeloblasts were found in the bone marrow at necropsy in more than normal numbers in a case of typical "agranulocytic angina" whose antemortem blood count was 200 white cells per c.mm. (all lymphocytes), *i. e.*, a marked absolute reduction of lymphocytes and absence of all other white cells.

2. Based on this and similar cases recorded in the literature, objection is raised to the current hypothesis of "granulocytic aplasia" as constituting the "primary" pathologic mechanism of

the disease, and in its place an hypothesis of "maturation arrest" is proposed for consideration and future study.

3. Inasmuch as there is an absolute reduction of lymphocytes in the blood stream as well as of neutrophils and on account of certain analogies with pernicious anemia, designation such as *pernicious leukopenia* is suggested as preferable to the more widely used names for this disease.

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## THE RESPONSE OF THE RETICULOCYTES TO IRON.

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The response of the reticulocytes in pernicious anemia to effective material gives information regarding the potency of the substance administered, the rate of rise of the red blood cells and the

desirable dose for a given case. It aids in determining whether the patient has difficulty in absorbing or utilizing the product when given orally and can thus lead to the advantageous use of a product given parenterally. Because this reaction has been shown to be of distinct value in pernicious anemia a study is being made of the response of the reticulocytes to iron in anemias that can be affected by this element.* Some of the information so far obtained from the oral administration of iron is presented here.

Data concerning positive reticulocyte responses have been obtained for over 100 cases, but only complete data for 66 cases and partial data for 20 additional cases first treated with maximal amounts of iron are for consideration at present. Those patients who have responded distinctly, but to varying degrees, to iron therapy include cases of anemia due to chronic blood loss with and without recent acute exacerbations, dietary defects, gastrointestinal disorders and pregnancy. Cases of ill-defined anemia, especially in women, and cases of idiopathic hypochromic anemia (simple achlorhydric anemia) are also included. In many cases more than one cause for anemia was present, including such complications as infections.

In cases of pernicious anemia without serious complications treated with maximal amounts of liver or potent substitute the height of the reticulocyte rise is inversely proportional to the level of the red blood cells directly before treatment. There is also a relation of the same sort between the hemoglobin level and the numbers of reticulocytes at the peak of their rise. Similar but less exact relationships exist for the anemias responding to iron, as is illustrated in Figs. 1 and 2. Each case was treated daily with from 3 to 4 gm. of ferrous carbonate or 4 to 6 gm. of iron and ammonium citrate. In all instances the hemoglobin and red blood cells increased to normal or to a very considerable degree. The patients were all adults, except for 2 children under 5 years of age, who had distinctly high reticulocyte responses. It is possible, owing to the character of the bone marrow in youth, that under comparable circumstances a relatively greater response of reticulocytes will occur in children than in adults.

Infections and other complications, such as pronounced arteriosclerosis, appear to hinder the action of iron just as they hinder the effect of potent material in pernicious anemia. Such conditions in the cases responding to iron appear to have played only a slight rôle in causing a more widely spread distribution of maximal reticulocyte rises than in comparable cases of pernicious anemia. However, the incidence of complications, especially infections, among the 16 cases with the lower reticulocyte rises for a given

* The iron salts administered were not purified, but were ones commonly prescribed which are usually contaminated with small amounts of copper and sometimes with other elements.

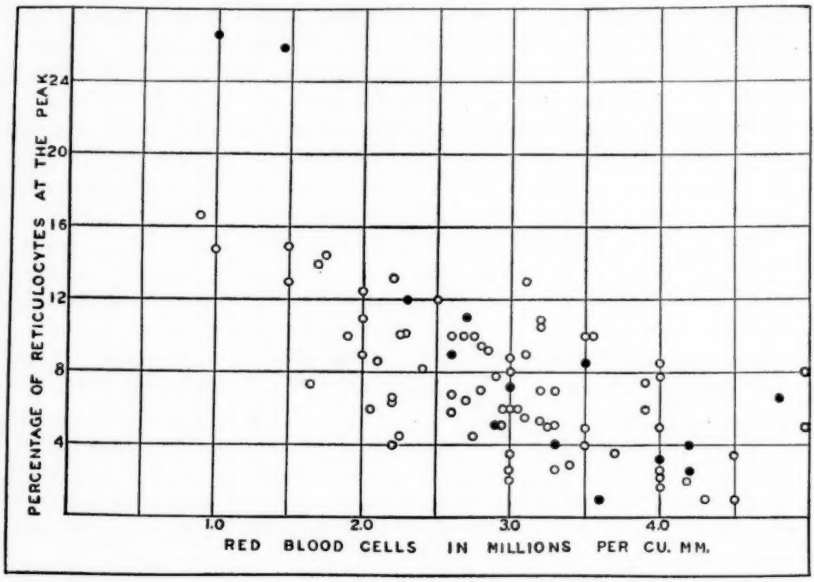


FIG. 1.—The relationship between the level of the red blood cells before treatment with iron and the percentage of reticulocytes at the peak of their rise. Each dot represents 1 case. The black dots represent uncomplicated cases of anemia due to chronic blood loss or to chronic dietary deficiency which manufactured blood in response to iron feeding at a maximal rate.

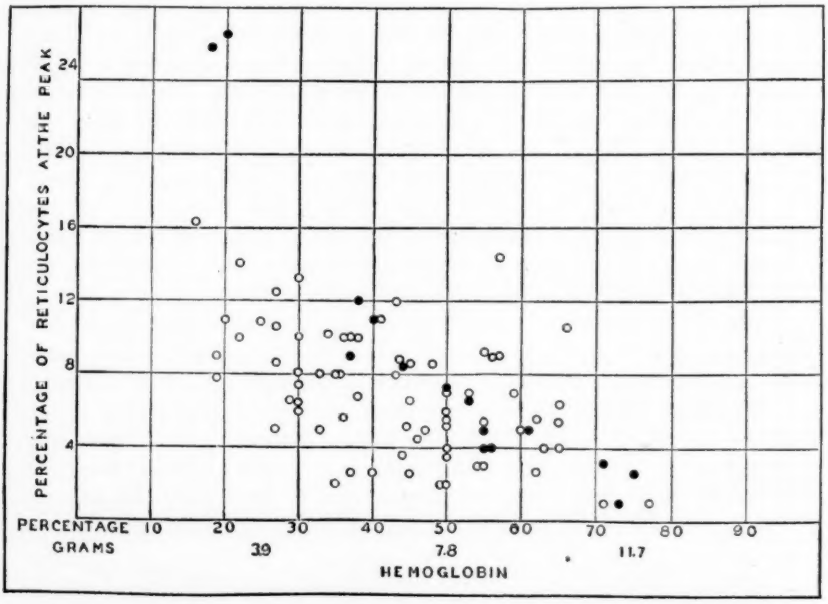


FIG. 2.—The relationship between the level of the hemoglobin before treatment with iron and the percentage of reticulocytes at the peak of their rise. Significance of dots as in Fig. 1.

red blood cell level below 3 million per c.mm. was four times as great as for the other 33 cases with comparable numbers of corpuscles. A similar state of affairs exists for a comparison with the hemoglobin level. When data were studied for uncomplicated cases of anemia due to chronic blood loss or chronic dietary deficiency (black dots, Figs. 1 and 2) responding to iron with maximal production of hemoglobin and red blood cells, it was found that the number of reticulocytes at the peak of their rise could be correlated more closely with the hemoglobin than with the red blood cell level. This becomes particularly evident in cases with distinctly low hemoglobin values and essentially normal red blood cell counts, so that distinct rises of reticulocytes occur in response to iron with red blood cell levels at which in pernicious anemia insignificant reticulocyte increases take place. Thus, in the types of anemia under consideration for a given red cell level above approximately 2.5 million per c.mm., a greater rise of reticulocytes occurs in response to maximal doses of iron than in pernicious anemia in response to adequate amounts of liver and allied products. It is rare to have uncomplicated cases of anemia responding to iron with red blood cells below 1.5 million per c.mm., so that a comparison at very low red blood cell levels is difficult to evaluate. However, with red blood cell levels below approximately 2.5 million per c.mm. the rise of reticulocytes in response to adequate therapy appears to be somewhat similar in the different types of anemia. On the contrary, in pernicious anemia with hemoglobin levels below about 10 gm. (64.1 per cent)* the rise of reticulocytes in response to adequate treatment is progressively greater than in "secondary" anemia. Below the level of about 5 gm. (32 per cent) hemoglobin the increase of reticulocytes in pernicious anemia is on the average at least double that which occurs in "secondary" anemia. This state of affairs suggested that in order to evaluate fully the reticulocyte response to iron, especially if the red blood cells are above 2.5 million per c.mm., there should be considered both the hemoglobin and red blood cell level. Data at hand suggest that relationships exist between the reticulocyte response and the corpuscular volume, hematocrit and state of the bone marrow, as told by the numbers and characters of the white blood cells; but these matters will not be discussed here.

An unselected series of 66 cases was divided into two groups according to whether the color index was below or above 0.66. (Fig. 3.) The mean red blood cell counts of each group were essentially the same, namely, 3.15 and 2.95 million per c.mm., respectively. The first group of 32 cases had a mean hemoglobin of

* Grams of hemoglobin indicate grams per 100 cc. of blood determined by the Sahli hemoglobinometer, allowing that 15.6 gm. of hemoglobin are equivalent to 21 volumes per cent oxygen capacity as determined by the van Slyke method. or 100 per cent hemoglobin.

5.3 gm. (34.2 per cent) and a mean color index of 0.54; the second group of 34 cases had a mean hemoglobin of 7.4 gm. (47.3 per cent) and a mean color index of 0.8. A plot of the daily average reticulocyte count after iron therapy was begun shows that the curve for the cases with the lower mean hemoglobin and color index rises faster and one-fifth again higher than for the cases with the higher mean hemoglobin and color index. A further survey of the relationships between the reticulocyte response to iron and the color index, red blood cell and hemoglobin levels is presented in Fig. 4.

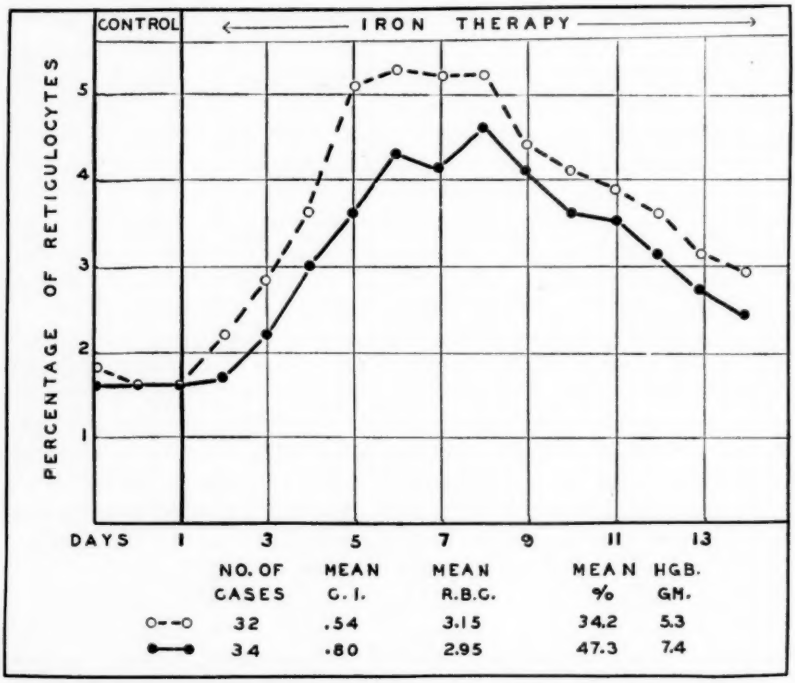


FIG. 3.—The mean response of the reticulocytes to iron in two groups of cases selected according to whether their color index was above or below 0.66.

As the figure shows, there is a similar relationship between the reticulocyte response and the color index in 26 of these 66 cases selected with approximately equal red blood cell counts between 2.5 and 3.5 million per c.mm. and divided according to whether the hemoglobin was above or below 6.9 gm. (44 per cent). However, when 18 cases were selected with approximately equal hemoglobin values averaging 6.4 gm. (41 per cent) and divided according to whether the red blood cells were above or below 3 million per c.mm., then a reverse state of affairs occurred so far as color index is concerned. The cases with the lower red blood cell counts

(average 2.61 million per c.mm.) had an average color index of 0.79 and those with the higher red cell counts (average, 3.83 million per c.mm.) had an average color index of 0.54, but the reticulocytes increase more in the former than in the latter group. The data show, of course, that cases may have the same color index, with the reticulocytes rising to very different numbers, dependent on the red blood cell and hemoglobin level.

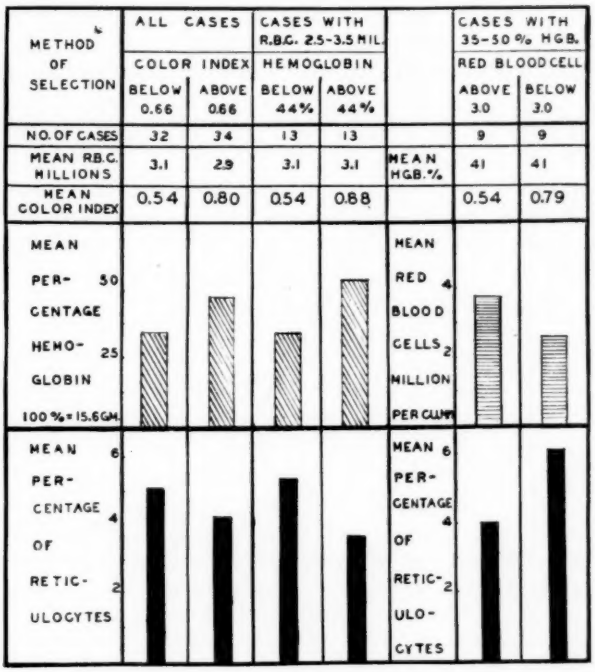


FIG. 4.—Mean maximal reticulocyte responses to iron correlated with color index, hemoglobin and red blood cell level.

It thus appears that for a given red blood cell level the reticulocyte response to maximal doses of iron will be greater the lower the hemoglobin, and the increase of reticulocytes will be greater for a given hemoglobin level the lower the red blood cell count. Although for pernicious anemia the distinctions are not so great, it appears from a special study of 58 uncomplicated cases that there is in this disease a tendency for the reticulocyte response at any given red blood cell or hemoglobin level to be slightly higher in direct proportion to the color index.

A case of anemia responding to iron may be considered more severe the lower both the hemoglobin and red blood cell level, and the patient with pernicious anemia with a rising color index is

relapsing. The height of the reticulocyte response to iron will be greater the lower both the hemoglobin and the red blood cells, and greater in pernicious anemia the lower the red blood cell level and the higher the color index at a given red blood cell level. This perhaps is because in pernicious anemia the need is primarily for cell production and apparently in anemias responding to iron it is particularly for hemoglobin production, although neither factor is

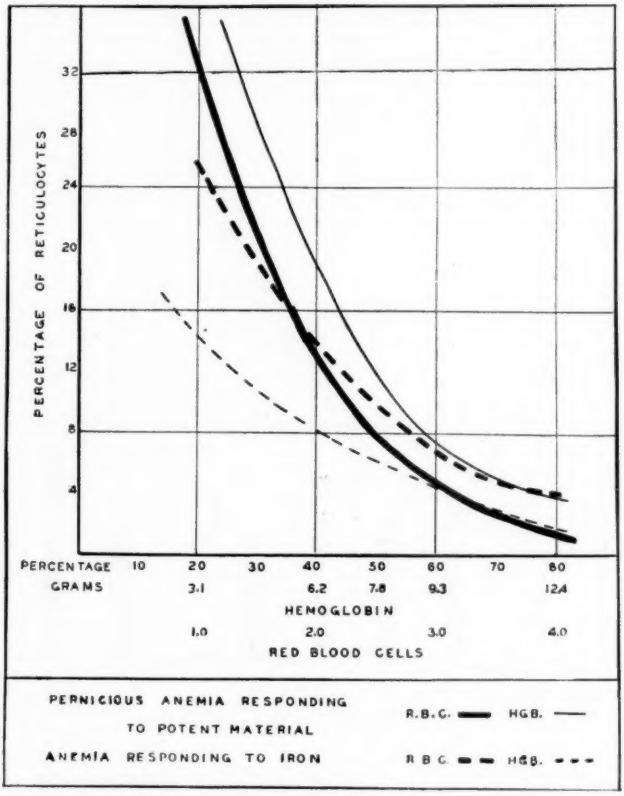


FIG. 5.—The trend of the reticulocytes at the peak of their rise in cases of pernicious anemia responding to potent material and in cases of anemia responding to iron. Red blood cell levels in millions per cubic millimeters and hemoglobin levels before treatment recorded as abscissæ.

independent of the other. Fig. 5 shows graphically in a broad way the relationships between hemoglobin and red blood cell levels and the percentage of reticulocytes at the peak of their rise in response to adequate therapy for pernicious anemia and for anemias responding to iron.

The divergent types of cases responding to iron play some rôle in the degree of the reticulocyte response. In evaluating the

response the exact type of case with its altered pathologic physiology should be considered, although the red blood cell and hemoglobin level are the most important factors in determining the level to which the reticulocytes will rise. Abnormality of the gastrointestinal tract and its contents can play an important rôle in the production of anemia. Castle and his associates[1] have shown the great etiologic significance of the lack of an undetermined factor in the stomach of pernicious anemia. Achlorhydria, especially when persistent after the administration of histamin, or defects associated with it, very probably enhances the development of many cases of anemia. Probably achlorhydria or defects which often accompany it favor the malabsorption or improper utilization of substances necessary for the maintenance of normal blood and other normal states.[2] Thus the response of the reticulocytes to iron in relation to achlorhydria has been considered. Apparently in cases with similar red blood cell and hemoglobin levels there is a definite tendency for those with achlorhydria to have a reticulocyte response to iron of less magnitude than cases with free hydrochloric acid in the gastric contents. Furthermore, data presented in Table 1 suggest that the former cases on the average increase the concentration of their erythrocytes and hemoglobin in response to iron more slowly than the latter, and this has been found true, especially when relatively small doses of iron are given. This is in accord with observations made by Witts,[3,4] who notes that cases of chronic microcytic anemia with achlorhydria respond to iron more slowly than cases of chlorosis and anemia due to blood loss with free hydrochloric acid in the gastric contents. These observations illustrate that the response of the blood elements to iron depend in a measure on the exact type of the anemic patient who is treated.

TABLE 1.—A COMPARISON OF THE RESPONSE TO IRON IN CASES OF ANEMIA WITH AND WITHOUT FREE HYDROCHLORIC ACID IN THE GASTRIC CONTENTS.

| | Free HCl. | No free HCl (histamin subcutaneously). |
|---|---|---|
| Number of cases | 24 | 24 |
| Mean red blood cells before treatment, millions per c.mm. | 3.1 | 3.2 |
| Mean hemoglobin before treatment, per cent | 42 | 42 |
| Mean reticulocytes at peak of response, per cent | 7.1 | 5.2 |
| Mean hemoglobin increase per day, per cent | 1.18 | 0.85 |
| Mean red blood cell increase per day, per c.mm. | 60,000 | 53,000 |

For the sake of clarity cases are selected so that the number of red blood cells and percentage of hemoglobin before treatment are similar in the two series. However, the cases which have been discarded show a difference in their response to iron similar to that shown in this table, in spite of the fact that the cases without free hydrochloric acid had on the average a much lower color index than the cases with free hydrochloric acid. The mean red blood cell and hemoglobin increase per day is determined in nearly all instances by averaging the total increases during the first 28 days following commencement of treatment. One hundred per cent hemoglobin is equivalent to 15.6 gm. per 100 cc. of blood.

The rate of manufacture of hemoglobin in cases responding to optimal amounts of iron and with an initial hemoglobin level of less than 6.2 gm. (40 per cent) can be predicted approximately from the level of the reticulocytes at the peak of their rise. This is illustrated by the data for 24 unselected cases presented in Fig. 6. The hemoglobin increased on the average 5.3 gm. (34 per cent) in 28 days. There is in general a direct relationship between the height of the reticulocyte rise and the rate of increase of hemoglobin.

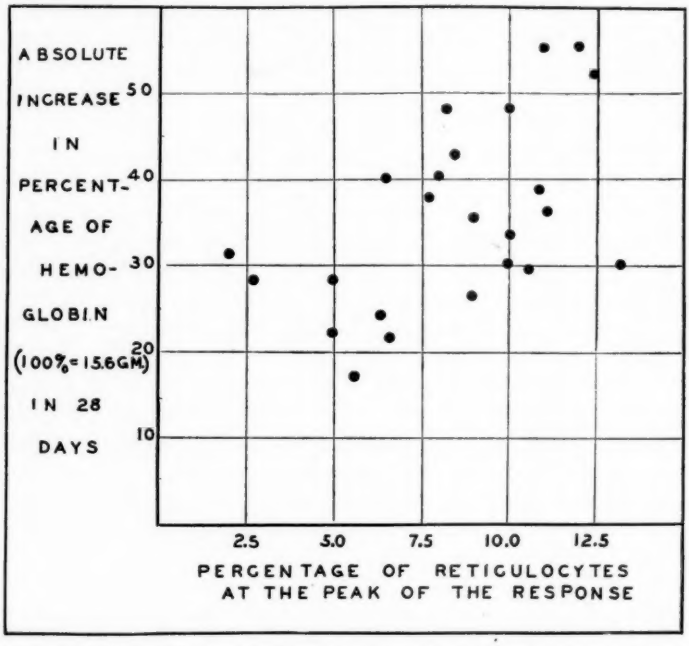


FIG. 6.—The direct relationship between the height of the reticulocyte rise and the rate of hemoglobin increase in 24 cases of anemia responding to optimal amounts of iron with an initial hemoglobin level of less than 6.2 gm. (40 per cent).

The character of the response of the reticulocytes as determined by the curve yielded from plotting the data obtained from daily reticulocyte counts may have biologic significance and may give information concerning pathologic physiology, treatment and prognosis. Fig. 7 gives examples of the course taken by the reticulocytes in response to maximal amounts of potent material for pernicious anemia and in response to maximal amounts of iron in anemia chiefly due to chronic blood loss. There is a tendency for cases responding to iron given daily by mouth to develop a reticulocyte response sooner than cases of pernicious anemia treated in a similar manner by potent material. The reticulocyte response to

iron occurs sooner in some cases than in others. There is also a distinct tendency of the curves for reticulocytes responding to iron to have more often flatter tops than those for pernicious anemia, so that frequently the reticulocytes occur in approximately the same numbers for 4 days at the height of their rise. A definite decrease for 1 or 2 days after a rapid rise to a maximum followed by an increase for 1 to 3 days of about equal magnitude to the former maximum occasionally occurs. Prolonged parabola-shaped curves,

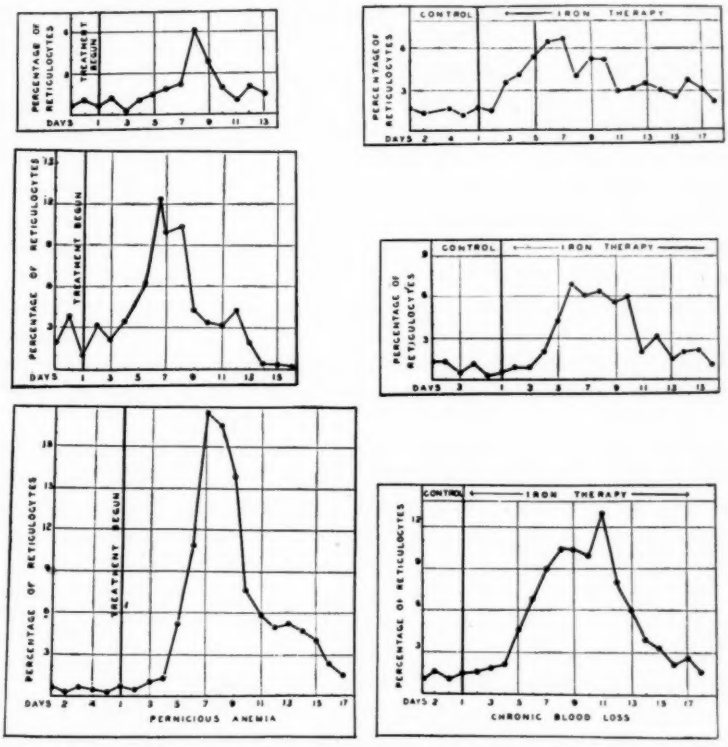


FIG. 7.—Examples of the course taken by the reticulocytes. The response to maximal amounts of potent liver preparations in 3 cases of pernicious anemia and to 6 gm. of iron and ammonium citrate fed daily in 3 cases of anemia chiefly due to chronic blood loss.

especially in cases with very low color indices and with approximately a normal number of red blood cells are not unusual and resemble the curves seen at times in pernicious anemia treated with suboptimal amounts of potent material. The duration of the reticulocyte response to iron usually lasts, however, about as long as in adequately treated cases of pernicious anemia, which is in the vicinity of 12 days. It is probable that more accurate comparisons of reticulocyte responses for their prognostic significance, relation to dose of potent material and the like could be made if considera-

tion was given to the total number of reticulocytes produced during the period of their response. That is to say, a response with a quick rise and fall of reticulocytes may not indicate as satisfactory a state of affairs, other things being equal, as a response with a sustained rise of reticulocytes which did not reach as high a level as in the former case. This has been referred to previously for pernicious anemia.[5] However, for practical purposes a consideration of the percentage or absolute number of reticulocytes at the peak of their rise gives useful information.

The study of the effects of iron include observations not only on the types of cases in which it may and may not be useful in promoting blood regeneration but also upon other matters such as dosage. No response to iron may be expected when anemia is primarily due, among other conditions, to infection, nephritis, scurvy, myxedema, true bone-marrow aplasia, metaplasia or megaloblastic hyperplasia as occurs in pernicious anemia. However, it must not be forgotten that some response to iron may occur in patients with such conditions because there may also exist anemia due to a condition that can respond to iron. The chief sorts of anemia that can respond to iron are those due to chronic blood loss, various sorts of dietary deficiency and altered gastrointestinal function, pregnancy and various types of chronic anemia of microcytic type without well-recognized cause, which are especially common in women.

The dosage of iron has been studied in various ways, especially by reticulocyte responses to varying amounts of iron in the same case. Although it is evident that small amounts of iron may accomplish distinctly beneficial results, it is also evident that large doses can accomplish the desired results when small doses cannot do so. This is especially true for cases of idiopathic hypochromic anemia (simple achlorhydric anemia) in which condition many, if not all, such patients must continue to take iron indefinitely after it has restored the blood to normal or else relapse ensues.

There are many ways of studying the multiple aspects of iron therapy. However, among other methods the course taken by the reticulocytes will be found serviceable, but such information must not be used alone, for the problems concerning anemia will be solved by bedside observations expanded in the laboratory. The observations must be made with strict accuracy and with the recognition that the scientific problem is associated with an appeal of immediate human interest.

**Summary.** A study is presented concerning *positive* reticulocyte responses to the daily oral administration of iron in maximal amounts to patients with anemia especially due to chronic blood loss, dietary defects, gastrointestinal disorders and pregnancy and to patients with chronic microcytic anemia of obscure origin.

The height of the reticulocyte rise is in general inversely proportional to the level of the red blood cells and hemoglobin directly

before treatment, but the relationships are less exact for the anemias responding to iron than for pernicious anemia in response to liver or potent substitute.

Infections and other complications hinder the action of iron similar to the way in which they hinder the effect of potent material for pernicious anemia.

Distinct rises of reticulocytes occur with low hemoglobin values in response to iron when the red blood cell level is one at which in pernicious anemia insignificant reticulocyte increases take place. With red blood cells above 2.5 million per c.mm. a greater rise of reticulocytes occurs in response to maximal amounts of iron than in pernicious anemia in response to adequate amounts of potent material; but when the red blood cells are below this number the reticulocytes rise in response to adequate therapy to a somewhat similar number in the different types of anemia. On the contrary, in pernicious anemia as the hemoglobin level decreases below about 10 gm. per 100 cc. of blood the rise of the reticulocytes becomes progressively greater than in "secondary" anemia, so that it is at least double when the hemoglobin is less than about 5 gm. per 100 cc. of blood.

Both the hemoglobin and red blood cell levels must be considered in evaluating the reticulocyte response to iron. For a given red blood cell level the reticulocytes will increase more the lower the hemoglobin and the increase of reticulocytes will be greater at a given hemoglobin level the lower the red blood cell count.

The exact type of case responding to iron plays a rôle in the degree of reticulocyte response. Cases with achlorhydria tend to have a slightly smaller response and to manufacture blood more slowly than comparable cases with free hydrochloric acid in their stomach contents.

The character of the curves yielded from plotting data obtained from daily reticulocyte counts in response to iron tend to differ somewhat from those obtained for pernicious anemia in response to liver or potent substitutes.

NOTE.—It is a pleasure to acknowledge our indebtedness to Dr. Chester S. Keefer and Dr. Leon G. Zerfas for supplying us with data on some cases.

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# REVIEWS.

THE INGENIOUS DR. FRANKLIN. Selected Scientific Letters of Benjamin Franklin. Edited by Nathan G. Goodman. Pp. 244; illustrated. Philadelphia: University of Pennsylvania Press, 1931. Price, $3.00.

WITH the passage of time no 18th century American figure looms larger than that of the great printer-philosopher-scientist-diplomat. The perennial interest in this fascinating personality is manifested, to be sure, in such works as "The True Benjamin Franklin," "The Medical Side of Benjamin Franklin," "The Many-sided Franklin," and so on; but with the exception of "My Dear Girl" (a charming series of letters to two young ladies in London), his own writings must still be sought in "ponderous volumes of collected works." The present series of 57 letters on a wide range of his scientific investigations and speculations is a desirable addition to Franklin-iana, especially when presented in such an attractive format. While excellent productions are perhaps only what we have come to expect from the best University Presses, we should not fail to appreciate how much the present revival in artistic bookmaking owes to these altruistic, nonprofit-making producers.

The letters selected, some of which have never been published before, include such timely topics as Daylight Saving, Electrical Treatment for Paralysis, Bifocals, Smallpox and Cancer, Cause of Colds, Sunspots, Toads Found in Stone and 5 on aërial navigation. They give ample evidence of the author's insatiable, constructive curiosity and the vitality of his mental processes, while his philosophic goal is indicated by such characteristic queries as "What signifies philosophy that does not apply to some use?" A list of additional letters and papers of general interest completes this highly entertaining volume. E. K.

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HARPER'S MEDICAL MONOGRAPHS, VOLS. I AND II. TREATMENT OF INJURY. By CLAY RAY MURRAY, M.D., F.A.C.S., Assistant Professor of Surgery, College of Physicians and Surgeons, Columbia University. Pp. 412; 196 drawings by the author. New York: Harper & Bros., 1931. Price, $5.00, 2 vols.

THIS seventh member of Harper's Medical Monograph series is a worthy fellow of its predecessors. Dr. Murray, in his effort to show the general practitioner "what to do" with injury, has written one

of the most practical manuals on traumatic surgery available in the English language.

His material is divided into five parts. Part I treats of injuries to soft parts. He gives full consideration to the too often neglected treatment of muscle, tendon, and bursal injuries, abdominal and chest injuries, and burns. In Part II he comes into his own in his treatise on fractures, except those of the spine and skull. The section is introduced by an excellent discussion of the general principles of fracture treatment, and is followed by a detailed description of individual fractures, illustrated by ample line drawings. The reader is taught and shown the various types of deformity which may occur at the same fracture site, and the author thereby emphasizes the importance of adapting the treatment to suit the individual needs of the fracture and patient. This portion of the book easily ranks as the equal of many larger works on fracture treatment.

Part III deals with dislocation and Part IV with spinal and cranial injury. The fifth part treats of miscellaneous trauma and includes joint injury, and foreign body wounds.

The publishers have recommended the work as particularly adapted to the needs of the general practitioner. It is more than that. It is a work which may be commended to all (surgeons, medical students, industrial physicians, etc.) who wish to easily learn the approved methods of the treatment of injury. Dr. Murray's lucid style makes an easy reading text, and the convenient size and binding of the volumes combine to make the set one well-worth having. L. F.

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PHYSICAL DIAGNOSIS. By WARREN P. ELMER, B.S., M.D., Associate Professor of Clinical Medicine, Washington University, St. Louis, and W. D. ROSE, M.D., Late Associate Professor of Medicine University of Arkansas, Little Rock. Pp. 903; 337 illustrations. Sixth Edition. St. Louis: The C. V. Mosby Company, 1930. Price, $10.00.

DR. ELMER, in revising Dr. Rose's work, has not only largely rewritten the book, but has also largely rearranged the material. So, in Part I, devoted to the technique of physical examination and normal physical findings, each diagnostic procedure is described for the whole body before taking up the next: *e. g.*, the inspection of the whole body is discussed before palpation is introduced. The book is primarily intended for teaching physical diagnosis to medical students, and for this purpose the book is altogether adequate. There is, however, no specific mention of the physical signs that may arise from foreign bodies in the air passages. A better grade of paper has served to improve the illustration over those of previous editions. R. K.

CHEMISTRY FOR NURSES. By HARRY C. BIDDLE, A.M., Instructor in Chemistry, School of Nursing, Western Reserve University. Pp. 336; 74 illustrations. Philadelphia: F. A. Davis Company, 1931. Price, $2.75.

THIS book, arranged as a textbook and laboratory manual, contains the important material that may be covered in the 45-hour period as recommended by the National League of Nursing Education.

Each chapter begins with a topical outline, and a series of questions that are bound to arise regarding the chemistry facts in the practice of nursing. These questions having aroused the interest of the student are answered in the subject matter following. Review questions and suggestions for reports and charts that may be used by those students able to go further, complete the lesson.

The laboratory exercises, both simple and practical with a few blank pages for personal notes, follow each lesson. An appendix containing miscellaneous chemistry facts, important to a nurse, and an index complete this text that is without doubt the best text in chemistry that we know of for nurses. M. S.

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A MANUAL OF PRACTICAL VERTEBRATE MORPHOLOGY. By J. T. SAUNDERS and S. M. MANTON. Pp. 220; 43 illustrations. New York: Oxford University Press, 1931. Price, $5.00.

THIS book is essentially a text and laboratory guide for beginners in comparative anatomy. Directions are given for dissection of various lower vertebrates and the pigeon, as well as the brain of a sheep. The figures accompanying these directions are so arranged that they may be colored. In the last three chapters the comparative anatomy of the vertebrate skull, teeth and the osseus system are considered. Investigators having need for a handy reference to the anatomy of the lower vertebrates will find this book of considerable value. H. R.

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THE INFANT WELFARE MOVEMENT IN THE EIGHTEENTH CENTURY. By ERNEST CAULFIELD, M.S., M.D. With a Foreword by GEORGE FREDERIC STILL, M.A., M.D. (CANTAB.), HON. LL.D. (EDIN.), F.R.C.P. (LONDON). Pp. 203; 8 illustrations. New York: Paul B. Hoeber, Inc., 1931. Price, $2.00.

CHILDREN are being well treated to-day from the medical history standpoint. No sooner had Ruhräh's Pediatrics of the Past become well settled in its proper niche than Still's History of Pediatrics arrived. This barely off the press when the present volume presents another aspect of the subject in an entertaining and instructive

manner. The rise of the infant welfare movement in England is especially well portrayed, whole chapters being given to Coram and the Foundling Hospital, William Cadogan, Hanway and George Armstrong (the author's special favorite). While the book does not pose as and should not be taken for a complete record of the movement, it has the stuff of real history and is a contribution well worth while.

E. K.

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LEHRBUCH DER ALLGEMEINEN PHYSIOLOGIE. By E. GELLHORN, PH.D., M.D., a. o. Professor of Physiology, Halle and Associate Professor of Physiology, University of Oregon. (With the collaboration of L. ASCHER, Bern, W. VON BUDDENBROCK, Kiel, C. OPPENHEIMER, Berlin, and J. SPEK, Heidelberg.) Pp. 741; 126 illustrations. Leipzig: Georg Thieme, 1931. Price, M. 49.50.

THE present volume covers, in what is on the whole a thorough and authoritative manner, the various subjects commonly included under the term "General Physiology." It comprises sections of 234 pages on the physico-chemical properties of the cell by its Editor, E. Gellhorn, 168 pages on the physiological chemistry and 27 pages on the energetics of cell processes by C. Oppenheimer, 172 pages on cellular morphology and the general physiology of development by J. Spek, 83 pages on the process of excitation by L. Ascher, and 44 pages on tropisms by W. von Buddenbrock. As far as the Reviewer is aware there have never previously been brought together in one place such detailed presentations of these various subjects. A volume of this sort is of value not merely from the practical standpoint of making accessible a very large amount of interesting material not hitherto treated in a single textbook, but also in giving the reader a broader and more correct view of the present scope of General Physiology than he is likely to obtain from most other similar sources. Particularly welcome is the inclusion of more physiological chemistry than is generally found in works in this field. The chief defect of the book in its present first edition is the absence of an authors' index and in some of its sections of sufficiently detailed references to the original literature.

M. J.

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MEDICAL JURISPRUDENCE. By CARL SCHEFFEL, PH.B., M.D., LL.B. Pp. 313. Philadelphia: P. Blakiston's Son & Co., Inc., 1931. Price, $2.50.

THE author of this book reverses the usual method; or, rather, looks at the whole subject from a point of view opposite to that which is common. Namely, instead of seeking to show the student how medical matters may effect or influence the solution of various

legal problems, he seeks to enable the student and physician to familiarize himself as to how legal factors effect him in the everyday practice of medicine and surgery and his standing as a sociologic factor in the community. Of course it is just as bad for a physician to endeavor to be his own lawyer as it is for anyone else and the author does not desire his book to be used for any such purpose. Altogether his work is well done. It is written in plain and simple English. There is no padding and it will be well for every young physician to study it; he would save himself from getting into trouble by so doing. C. B.

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DYNAMIC RETINOSCOPY. By MARGARET DOBSON, M.D., LOND. Pp. 56; 11 illustrations. New York: Oxford University Press, 1931. Price, $2.50.

THE apparent purpose of this monograph is to champion the advantages of refracting without a cycloplegic, and, therefore, will have an immediate appeal to those who are so minded, or schooled, to begin with. By the same token it may not appeal to others who consider a cycloplegic necessary. Although titled Dynamic Retinoscopy only eleven pages of a total of fifty-five deal with this subject; the other chapters being a consideration of retinoscopy in general, muscle balance and accommodation and convergence.

The price is excessive. F. A.

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DISEASES OF THE GUMS AND ORAL MUCOUS MEMBRANE. By SIR KENNETH GOADBY, K.B.E., M.R.C.S., L.R.C.P., D.P.H. (CANTAB.), Lecturer on Bacteriology of the Mouth, Dental Department, University College Hospital. Pp. 496; 146 illustrations. Fourth Edition. New York: Oxford University Press, 1931. Price, $13.00.

THE contents of this book are far more comprehensive than indicated by the title. In addition to disease of the gums and oral mucous membrane proper, the author deals extensively with dental caries and its sequelæ—dento-alveolar abscess, acute and chronic, diseases of the alveolo-dental articulation (pyorrhea alveolaris), tumors of the jaws, neuralgia and mouth neuroses. His principal object is to keep before the reader the relationship of infection and disease in the mouth to diseases of the body as a whole. Special attention is called to the chapters on diseases originating from mouth infection and on diseases with oral symptoms. The author's views are to be regarded as sane and reliable when evaluating the importance of oral infection as related to disease elsewhere in the body, and the internist will find in the book a valuable guide in this respect. Aside from a few reproductions of Roentgen ray films, the illustrations are excellent. R. I.

# BOOKS RECEIVED.

## NEW BOOKS.

*A Textbook of Laboratory Diagnosis.* By EDWIN E. OSGOOD, M.A., M.D., Assistant Professor of Medicine and Biochemistry, Director of Laboratories, University of Oregon, School of Medicine, and HOWARD D. HASKINS, M.D, Professor of Biochemistry, University of Oregon, School of Medicine. Pp. 475; 21 figures and 6 colored plates. Philadelphia: P. Blakiston's Son & Co., 1931. Price, $5.00.

*The Thomsen Hemagglutination Phenomenon.* By V. FRIEDENREICH. Pp. 138; illustrated. Copenhagen: Levin and Munksgaard, 1930.

*Approved Laboratory Technic.* Prepared under the Auspices of The American Society of Clinical Pathologists. By JOHN A. KOLMER, M.D., DR.P.H., D.SC., LL.D., Professor of Pathology and Bacteriology, Graduate School of Medicine, University of Pennsylvania, and FRED BOERNER, V.M.D., Associate Professor of Bacteriology, Graduate School of Medicine, University of Pennsylvania; Assisted by C. ZENT GARBER, A.B., M.D., Associate in Pathology, Peking Union Medical College, and Committees of The American Society of Clinical Pathologists. Pp. 663; 300 illustrations, 11 plates. New York: D. Appleton & Co., 1931. Price, $7.50.

*Phantastica, Narcotic and Stimulating Drugs.* By LOUIS LEWIN. Pp. 335. New York: E. P. Dutton & Co., 1931. Price, $3.75.

*The Conquest of Old Age.* By PETER SCHMIDT, M.D., Translated by EDEN and CEDAR PAUL. Pp. 307; 40 plates. New York: E. P. Dutton & Co., 1931. Price, $5.00.

*A Life of Joseph Priestley.* By ANNE HOLT. With an Introduction by FRANCIS W. HIRST. Pp. 221; 1 illustration. New York: Oxford University Press, 1931. Price, $3.50.

*Transactions of the Association of American Physicians, vol. 46, 1931.* Pp. 379; illustrated.

*The Ingenious Dr. Franklin.* Selected Scientific Letters of Benjamin Franklin. Edited by NATHAN G. GOODMAN. Pp. 244; illustrated. Philadelphia: University of Pennsylvania Press, 1931. Price, $3.00. For review see p. 122.

*Medical Psychology.* Monograph Series No. 54. By WILLIAM A. WHITE. Pp. 141; 4 illustrations. Washington, D. C.: Nervous and Mental Disease Publishing Company, 1931.

*The Commoner Nervous Diseases.* By FREDERICK J. NATTRASS, M.D. Dunelm., F.R.C.P. London, Assistant Physician, Royal Victoria Infirmary, Newcastle-upon-Tyne. Pp. 218; 15 illustrations. New York: Oxford University Press, 1931. Price, $4.00.

*Guy's Hospital Reports, Vol. 81 (Vol. 11, Fourth Series), No. 3, July, 1931.* Edited by ARTHUR F. HURST, M.D., Assisted by various contributors. Pp. 123; illustrated. London: The Lancet Limited, 1931. Price, 12s. 6d. per issue.

*Infections of the Kidney.* By MEREDITH F. CAMPBELL, M.D., F.A.C.S., Attending Urologist, Babies Hospital, New York Nursery and Child's Hospital; Assistant Visiting Urologic Surgeon, Bellevue Hospital, New York. Pp. 343; 40 illustrations. New York: Harper & Brothers, 1931. Price, $3.00.

*A Description of the Planes of Fascia of the Human Body.* By B. B. GALLAUDET, Department of Anatomy, College of Physicians and Surgeons, Columbia University, New York. Pp. 75. New York: Columbia University Press, 1931. Price, $2.00.

*The Black Death and Men of Learning.* By ANNA MONTGOMERY CAMPBELL, Assistant Professor of History, New Jersey College for Women. Pp. 210. New York: Columbia University Press, 1931. Price, $3.00.

*The Medical Clinics of North America, Vol. 15, No. 3 (Chicago Number, November, 1931).* Pp. 227; 53 illustrations. Philadelphia: W. B. Saunders Company, 1931.

*How's Your Blood Pressure?* By CLARENCE L. ANDREWS, M.D., Attending Physician and Medical Chief at the Atlantic City Hospital. Pp. 225. New York: The Macmillan Company, 1931. Price, $2.50.

*The Ethno-Botany of the Maya.* Publication No. 2 of The Tulane University of Louisiana, Middle American Research Series. By Ralph L. Roys. Pp. 359. New Orleans: The Department of Middle American Research, The Tulane University of Louisiana, 1931.

*Typhoid Fever.* By WILLIAM BUDD, M.D., F.R.S. Pp. 184; 5 illustrations, 1 in color. New York: American Public Health Association, 1931. Price, $5.00.

*Experimental Studies on the Course of Paratyphoid Infections in Avitaminotic Rats.* By H. C. A. LASSEN. (Translated from the Danish by HANS ANDERSEN, M.D.) Pp. 248; illustrated. Copenhagen: Levin and Munksgaard, 1931.

*Blood Sugar in Normal and Sick Children.* By ELISABETH SVENSGAARD. Pp. 245; illustrated. Copenhagen: Levin and Munksgaard, 1931.

*The Truth About Birth Control. Pamphlet No. 4.* By NORMAN E. HIMES. Pp. 28. New York: The John Day Company, 1931. Price, 25 cents.

## NEW EDITIONS.

*Elementary Anatomy and Physiology.* By MARY REES MULLINER, M.D., Director of the American School for Physical Education. The Physical Education Series. Edited by R. TAIT MCKENZIE, M.D., M.P.E., LL.D., Professor of Physical Education and Physical Therapy, University of Pennsylvania. Pp. 448; 313 engravings in black and color. Third Edition, thoroughly revised. Philadelphia: Lea & Febiger, 1931. Price, $4.75.

A useful book for students of physical education and nurses who do not desire a large general textbook which necessarily includes considerably more material than they have time to digest. In this edition the physiology of the various systems has been more fully treated and numerous other details brought up to date by consulting the last editions of Gray's Anatomy and Starling's Physiology.

*The Physiology of Muscular Exercise.* By the Late F. A. BAINBRIDGE, M.A., M.D. Cantab., D.Sc., F.R.C.P., F.R.S., Professor of Physiology, University of London. Rewritten by A. V. BOCK, M.D. Harvard, PH.D. Cambridge, Assistant Professor of Medicine, Harvard; Physician, Massachusetts General Hospital, Boston, and D. B. DILL, PH.D. Stanford, Assistant Professor of Biochemistry, Harvard. Pp. 272; 46 illustrations. Third Edition. New York: Longmans, Green & Co., 1931. Price, $5.00.

*Medical Electricity for Students.* By A. R. I. BROWNE, Member of the Society of Radiographers; Radiographer at the Royal Alexandria Infirmary. Pp. 245; 88 illustrations. Third Edition. New York: Oxford University Press, 1931. Price, $4.00.

# PROGRESS
OF
# MEDICAL SCIENCE

## MEDICINE

UNDER THE CHARGE OF
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AND
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**A Note on the History of Pellagra in the United States.**—It is of interest to note that it was not until 1907 that pellagra was recognized in the South. In spite of the fact that the disease was not known, WHEELER (*U. S. Pub. Health Rep.*, 1931, **46**, 2223) contends that pellagra was present in the United States and that the only argument against the incidence of pellagra in the South to any considerable extent prior to its recognition in 1907–1908 was the fact that it was not so recognized. He calls attention to the fact that in the first seven editions of Osler's *Practice of Medicine* the statement was made that it has not been observed in the United States. Other standard textbooks of the time make no reference to pellagra. However, when this very common disease in the South was recognized a group of older practitioners of medicine were circularized for the purpose of asking them whether or not they had seen cases before this particular period, and it was found that a goodly number of them had observed the disease but did not know what it was. This fact alone would destroy one of the arguments of those who contend that the disease is of bacterial origin. One of the reasons advanced that the disease is primarily bacterial is that there was an epidemic of pellagra in 1907–1908; such an epidemic the epidemiologists believed could occur only when the disease is a disease transmitted from man to man. Observations that have been made on the incidence of pellagra in recent years have shown that the disease is very much more prone to occur in large numbers following periods of economic stress. Such a period existed in 1907–1908. Likewise, there have been known increases of the disease in 1915, 1921 and 1930. At the present time in Louisiana, which probably holds good in other southern States, more pellagra has been reported than any time in recent years. As a matter of fact, in the 6 weeks' period, beginning

June 30, more cases were reported than of any other of the reportable diseases, exceeding by far the next disease in frequency. These data may be taken to substantiate the idea that dietary inadequacy plays some rôle in the production of the disease. It is reasonably obvious why the diet should be inadequate following periods of financial depression. Incidentally, it may be mentioned that only from 10 to 15 per cent of the pellagra cases in a given community will consult a physician. These data have been obtained through field surveys in localities where pellagra is prevalent and where the entire population has been studied. Another observation made by this writer seems worthy of recording, and that is that it is only the out-spoken cases of pellagra who have the diagnostic triad of dermatitis, diarrhea and dementia and it is only such cases that are actually reported to the health authorities.

## SURGERY

UNDER THE CHARGE OF
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**Acute Craniocerebral Injuries.**—OCHSNER (*Am. J. Surg.*, 1931, **12**, 523) belives that edema of the brain is the most important pathologic lesion as it is the most frequently encountered. The extent of the edema varies considerably. Not infrequently a vicious circle is produced, *i. e.*, as a result of the edema there is interference with the venous return, which causes a diminished absorption of the cerebrospinal fluid, which in turn produces an increased intracranial pressure. Contusion and laceration are found in the more extensive injuries of the cerebrum and vary largely in degree. Lacerations are usually associated with lesions of the cranium, whereas contusions frequently are not. Hemorrhage is of two types, intradural and extradural. Associated with every cerebral injury from the slightest contusion to the extensive laceration, there are varying degrees of hemorrhage. Intradural hemorrhage is a result of injury to the brain substance, whereas extradural hemorrhage occurs as a result of injury to the middle meningeal artery or rarely to the lateral venous sinus. Subdural hemorrhage is of importance because of sequelæ which may develop such as sterile meningitis, abnormal accumulation of cerebrospinal fluid, which may subsequently lead to cerebral atrophy and localized cystic changes occurring in hematomas. Fractures of the skull are divided into two main types, those of the vault and those of the base. Simple and comminuted fractures of the vault are of no significance clinically. Fractures of the base are of great significance because almost invariably they are compound fractures in that fracture extends into the nose, nasal accessory sinuses, mastoid process, or middle ear. The finding of blood in the cerebrospinal fluid is of utmost importance because of the subsequent sequelæ which may develop, because of the blood in the subarachnoid space. The treatment is one of conservatism basically.

**Mesenteric Vascular Occlusion.**—LARSON (*Surg., Gynec. and Obst.*, 1931, **53**, 54) says that the most common causes of arterial embolism were mural cardiac thrombi. The most common causes of arterial thrombosis were arteritis and arteriosclerosis of the mesenteric artery. Venous mesenteric occlusion most often resulted from a septic process either in the gastrointestinal tract or the pelvis and was of the ascending type. It followed hepatic disease in 25 per cent of cases. The vascular occlusion affected the arteries in 14 cases, the veins in 16 and both veins and arteries in 6. In all cases of arterial occlusion and in all but one of the cases of venous occlusion, the superior mesenteric vessels were involved. A definite source of the vascular occlusion either was unknown or was problematic in 8 of the 36 cases. Hemorrhagic infarction resulted in 31 of the 36 cases. When intestinal infarction took place, it was generally manifested by symptoms of intestinal obstruction which were indistinguishable from those of other types of obstruction. Typically it occurred in an elderly person, starting with extremely severe colicky abdominal pain, nausea, vomiting and diarrhea. The vomitus and the diarrheal stool were often mixed with blood; occasionally complete retention of feces was noted. Soon the pain became steady, the shock more severe, the abdomen distended and tympanitic and the temperature and pulse, which at first were likely to be subnormal, became progressively elevated. Later signs of general peritonitis developed and death took place. The symptoms produced by closure of the main trunk were indistinguishable from those produced by obstruction of the branches. The course of the disease is short and may be less than 48 hours. In at least 53 per cent of the cases definite peritonitis was present and in 55 per cent bloody ascites was noted.

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**Autointoxication and Shock.**—MASON and LEMON (*Surg., Gynec. and Obst.*, 1931, **53**, 60) ssate that fresh tissue extract administered intravenously lowers blood pressure sufficiently probably to endanger patients who are in a critical condition. Fresh tissue extract is a very potent factor in producing intravascular coagulation and sublethal doses of autolyzed liver-tissue extract causes marked circulatory disturbances; the lethal dose being 7 to 8 cc. for the dog. Treatment of autolyzed liver-tissue extract with tannic acid does not precipitate the toxic fraction. The marked rise in blood pressure following sublethal doses of autolyzed tissue suggests the possibility that foci of infection may liberate a toxic substance which elevates blood pressure.

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**Acute Gonococcal Epididymitis.**—GARVIN (*Am. J. Surg.*, 1931, **12**, 502) says that gonococcal epididymitis is the most frequent disease of the testicle and the most prominent cause of male sterility. Chemical irritation, instrumental trauma and sexual excitement with an overdistended bladder in the presence of either an active or latent gonococcal infection, are the most common causes of epididymitis. Epididymitis is the result of a mechanical transference of gonococci-laden pus from the posterior urethra and seminal vesicles down to the vas to the epididymis. It is peritubular extension and not intratubular, involving principally the globus minor and other portions of the epididymis by periepididymal extension. It is a true epididymitis and not an epididymo-orchitis. Clinical experience leads to the belief that

in the vast majority of cases conservative treatment, rest, scrotal splintage, intramuscular injections of nonspecific protein will yield good results, many cases remaining ambulant. Operative treatment is indicated in the fulminating cases not yielding to conservative treatment and in recurrent cases and in cases not resolving. Thorough eradication of all foci of infection in the posterior urethra, prostate and vesicles is necessary regardless of type of treatment employed.

## THERAPEUTICS

UNDER THE CHARGE OF
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AND
SOMA WEISS, M.D.,
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**Treatment of Muscular Rheumatism by Infiltration of Glucose Solution.**—Long having recognized the unsatisfactory results obtained from the use of a wide variety of medicinal agents, heat, massage and the like, NATANNSEN (*Deutsch. med. Wchnschr.*, 1931, **57**, 885) experimented with the infiltration of the painful areas by means of local anesthetics in various solutions. He found that a 10 per cent solution of glucose or a mixture of glucose and fructose was almost specific in the relief of pain, being both immediate and lasting in its effects. The author here presents a brief report on the basis of 5 years experience with the 10 per cent sugar solutions. He states that its response to the wide infiltration of the subcutaneous and muscular tissues lying within the painful zone with amounts ranging from 30 to 100 c.cm. is so certainly effective that the failure of the pain to disappear is almost diagnostic in the sense that it indicates some other condition than muscular rheumatism or myalgia as the cause of the pain. Relapses are exceedingly rare and are almost always of extremely brief duration. The method of action is not clear and is not entered into in this place by the author. He suggests, however, that the effects may be due to combined osmotic chemical and mechanical actions. No deleterious effects have been observed. The method is naturally contraindicated in diabetic patients.

**The Action of Strophanthin on the Circulating Blood Volume.**—Investigations carried out upon patients suffering from decompensated valvular heart disease under conditions of control and with the employment of the trypan-red method of determining blood volume led MIES (*Ztschr. f. Krebsforsch.*, 1931, **33**, 460) to the conclusion that strophanthin diminishes the blood volume to a significant degree for from 24 to 36 hours after its intravenous administration. The degree of reduction of blood volume is more or less proportional to the size

of the dose administered. Similar results were obtained from another digitalis body, adovern, indicating the possibility that this is a characteristic of the action of this whole group of drugs. The author suggests that the diminution in blood volume may possibly be a factor in aiding restoration of cardiac efficiency by reducing venous congestion, but he does not feel prepared yet to express an opinion upon the worth of this suggestion.

## PEDIATRICS

UNDER THE CHARGE OF

THOMPSON S. WESTCOTT, M.D., AND ALVIN E. SIEGEL, M.D.,

OF PHILADELPHIA.

**Thyroidectomy for Thyrotoxicosis in the Young.**—GREENE and MORA (*Surg., Gynec. and Obst.*, 1931, **53**, 375) report 26 cases in which thyroidectomy was done for thyrotoxicosis in children between the ages of 8 and 16 years. These cases were a part of a series of 1200 consecutive toxic goiter patients who were subjected to operation. There were 22 girls and 4 boys. The chief symptoms and signs were tachycardia, nervousness, goiter, exophthalmos, tremor, loss of weight, palpitation, enlargement of the left side of the heart, irritability, weakness and restlessness. The symptoms corresponded closely to those manifested in adults. The average pre-operative systolic and diastolic blood pressure readings were 132 and 65 mm., respectively. The average postoperative readings were 108 and 72 mm. The average pulse pressure dropped from 67 to 36 mm. after operation. The average pre-operative basal metabolic rate was +34.6. The average postoperative reading was −6.2. All of th glands examined microscopically showed varying degrees of hyperplasia and hypertrophy. One-stage thyroidectomy was done in every instance, with no fatalities.

**The Retention Rate of Calcium: Phosphorus in Infants and Children.**—STEARNS (*Am. J. Dis. Child.*, 1931, **42**, 749) from a consideration of the rate of growth of the various tissues of the body from birth to 1 year of age, and the distribution of phosphorus between the bony and the soft tissues, it is considered that a retention ratio of calcium: phosphorus of between 1.5 to 1 and 2 to 1 is normal for an infant. A retention ratio lower than 1.5 to 1 indicates a more rapid growth of soft tissue than of bone. A ratio of 2 to 1 or more is considered as probably indicative that a calcium shortage in the body is being corrected. From the reported retention of calcium and phosphorus in artificially fed infants, a retention of at least 40 mg. of calcium and from 20 to 25 mg. of phosphorus per kilogram of body weigh per day is considered desirable for artificially fed infants. The ratio of retained calcium to phosphorus will be somewhat lower in older children than in infants because of the great increase in the relative amount of muscular tissue during childhood. In a normal child, it is considered that the retention rate will

probably be lower than that observed in infants, but it should be greater than 1 to 1. In older children the absolute retention of calcium and phosphorus per kilogram of body weight may be expected to decrease with the age of the child. A retention of at least 10 mg. of phosphorus per kilogram of body weight per day is desirable even in older children. The retention of calcium should be at least equal to the retention of phosphorus. Retentions of calcium and phosphorus of less than 10 mg. per kilogram of body weight are probably not optimal in very young children.

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**Treatment of Toxicosis With the Aid of a Continuous Intravenous Drip of Dextrose Solution.**—KARELITZ (*Am. J. Dis. Child.*, 1931, **42**, 781) treated 21 patients with severe toxicosis by this method and only 3 died, which was a mortality of only 14 per cent. Four patients, who were severely toxic and presented evidence of severe pneumonia before treatment was started, also died. Five other patients who were very toxic but in whom it was not possible to make a diagnosis of toxicosis recovered under this treatment. In the entire group of 30 cases there were 7 deaths or a mortality of 23 per cent. The author believes that the administration of fluid by the continuous intravenous method is a definite improvement in the treatment. The withholding of milk for a longer time, which he believes is as important as any other phase of the treatment, is thus made possible. The entire requirement of fluid is given through the one cannula with the least disturbance of the child. Acidosis and concentration of the blood respond rapidly to this form of treatment. It supplies water, salt and dextrose in a hypertonic solution at a rate fast enough to produce diuresis at first, and later slow enough to permit proper assimilation. Blood, epinephrin, caffein and digitalis can be given through the same cannula. During the time of the intravenous flow, the gastrointestinal tract, as well as the entire body, is given a much needed rest. Quiet sleep usually ensues, vomiting usually stops, thirst is created, and in many cases the diarrhea is favorably influenced. The child is spared the pain of the subcutaneous injection of the fluid and the occasional complication resulting from intraperitoneal injection, and the doubt of its absorption is obviated. The author confirms the opinion of Schick that the requirement of fluid is much less than is customarily thought to be. Certain facts must be constantly kept in mind. Treatment must be radical and prompt as soon as diagnosis is made. Supportive treatment, such as the administration of epinephrin and caffein, should be given as indications arise. All cases of toxicosis should be considered as severe. The intravenous administration of dextrose and transfusion should be employed promptly, and the minimum period during which milk should be withheld should be from 24 to 48 hours, or until detoxification is complete. Once the feeding of milk is commenced it should be given in small amounts of from 5 to 10 cc., and increased slowly. When there is a relapse, treatment should be started again from the beginning with the intravenous method of administering dextrose, transfusion of blood and abstinence from milk. Patients with intercurrent infections especially otitis and abdominal distention should be treated actively.

**Skin Temperatures of Children.**—Talbot (*Am. J. Dis. Child.*, 1931, 42, Part II) made studies of skin temperatures in children by means of a thermocouple. There is a local variation of the temperature of the skin over different parts of the body, even in normal children; the temperature of the trunk being highest, the face next and the extremities lowest. The temperature of the feet tends to be lower than that of the hands. Surrounding temperature has a definite effect on the temperature of the skin of the body even when it is clothed. The cooler the room the lower the temperature of the skin. There is also a seasonal effect on the temperature of the skin. This study showed that humidity within the limits of room temperature and room humidity had no effect on skin temperature. There is a rapid loss of heat from the surface of the body on exposure. This affects the face least, the body next and the extremities most. There is a greater variation in the reaction of the extremities to different surrounding temperatures than in other parts of the body. This suggests that the extremities act as safety valves for the conservation or elimination of heat. During fasting the temperature of the skin, as well as that of the body becomes reduced. Exercise has a very definite effect on the skin temperature. During the first few minutes of exercise the temperature of the skin falls and later rises. This may be of profound physiologic importance, and suggests that when exercise is first commenced heat is retained in the body in order to increase the efficiency of the muscles. This study gives further evidence that the heat-regulating apparatus of the premature infant is not developed. The temperature of the skin, as well as that of the body, is affected directly by the surrounding temperature and to a greater degree than in normal babies. Studies were made of the effect of fever on subjects with different body temperatures. These were grouped in such a way that the skin temperature for different fevers and different room temperatures are now available and are presented as possible standards of expected skin temperatures for different body and room temperatures. The skin temperature was recorded for a number of cretins with lowered metabolic rates. Some of them were studied after the metabolism had been elevated by the use of thyroid gland. When heat production was found increased, the temperature of the skin was increased.

## GYNECOLOGY AND OBSTETRICS

UNDER THE CHARGE OF

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**Ovarian Hormone Therapy.**—The results obtained in treating 63 cases of ovarian deficiency, as evidenced by amenorrhea of various types with a water soluble ovarian preparation known as "oestrin"

have been described by SMITH (*Lancet*, 1931, **220**, 464). He gives a course of daily hypodermic injections of 10 units for from 6 to 18 days, often repeating the course if no results were obtained from the first series. In cases of primary amenorrhea the results were negative. These were individuals who had passed the normal age of puberty without any signs of the onset of menstruation. In primary menstrual irregularity, menstruation became regular in 6 out of 19 cases. These were individuals in whom menstruation had never occurred from the onset at less than 3 or 4-month intervals. The best results of the entire series were obtained in cases of secondary amenorrhea which developed after some years of regular menstruation. In these cases positive results were obtained in 20 out of 37 cases (54 per cent). In 12 of the successfully treated cases the subsequent rhythm of menstruation was normal without any further treatment and in 2 of these patients, who had been sterile, pregnancy subsequently occurred.

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**Leukoplakic Vulvitis.**—This curious, annoying and sometimes dangerous condition has been discussed by COUNSELLER (*Minn. Medicine*, 1931, **14**, 312), of the Mayo Clinic, who states that in the early stages the treatment usually consists of the use of emollients and salves, which have however, only a temporary effect. Roentgen rays and radium often stimulate the disease and may produce a burn. If a malignant lesion is not present, he believes the ideal treatment consists of sectioning the internal pudic nerve, thereby anesthetizing the vulva and permanently relieving the pain and pruritus, which are so constant and so annoying in this condition. This has been done at the Mayo Clinic with very satisfactory results although they make no claim for the originality of the procedure. Following the operation the patient should be submitted to careful examination at least twice a year and if there is any question as to the presence of a malignant lesion, simple vulvectomy should be performed in cases in which the malignancy is graded 1 or 2. If the tumor is of a higher grade of malignancy or if there is lymphatic involvement in a case of lower grade malignancy, radical vulvectomy with bilateral dissection of the gland-bearing area should be performed. If the condition of the patient in whom a malignant neoplasm is found does not justify radical removal, then he advises section of the internal pudic nerve and the use of radium as palliative measures.

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**Carcinoma of Female Urethra.**—In spite of the fact that the reports in the literature indicate that the results of treatment of carcinoma of the urethra by operation show less than 20 per cent living patients at the end of a year, MIKULICZ-RADECKI (*Zentralbl. f. Gynäk.*, 1931, **55**, 2922) sounds a bit optimistic over the results which have been obtained in Stoeckel's Clinic in Berlin. They have treated these cases by means of a combined technique, taking into account not only the primary tumor but also the regional lymphatic glands. The primary tumor is treated with radium irradiation, the maximum dose being 2000 mg.-hrs., although in the less advanced cases 1000 mg.-hrs. may be sufficient. The glands in the inguinal region and along the large pelvic vessels are removed surgically whenever possible. Of 4 cases which he has treated by this method all are living over a year after the treatment, 3 of them living from $1\frac{1}{2}$ to 3 years completely free from recurrence and with complete urinary continence.

# OPHTHALMOLOGY

UNDER THE CHARGE OF

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**Retinal Changes in Hypertension and in Renal Disease.**—According to ROLFE (*Arch. Ophthal.*, 1931, **6**, 433), the lesions seen in the eye grounds of patients with hypertension and renal disease consist of various combinations of vessel changes with hemorrhages, "hard white" and "cotton wool" patches, and edema of the retina and of the optic disc. The vessel changes may be either spastic constriction or sclerosis of the arteries or dilatation of the veins. Histologically, in the eyes of people who have died of nephritis, edema is found in the optic nerve and edema and hemorrhages in the various layers of the retina between the retina and the choroid. Sclerosis of the retinal arteries may or may not be present. When present it is similar to sclerosis elsewhere. The white patches seen ophthalmoscopically are represented by various types of degeneration of the retinal tissue—varicosities of a group of nerve fibers, lipid deposits in the retinal tissue, areas of destruction of retinal tissue with fat or fibrous deposits and with large phagocytic cells filled with fat. The histologic changes are essentially the same in retinitis of hypertension. Renal lesions may be classified into three main groups: nephrosis, glomerulonephritis and renal sclerosis, which last may be benign or malignant. In nephrosis retinal lesions do not occur, since all the changes found in the retina and its vessels in diseases of the kidney are due primarily to hypertension. Destruction of kidney tissue in itself does not cause retinal changes. Hypertension probably causes sclerosis of the retinal arteries, and, through ischemia, the result of spasm or sclerosis or both, the retinal degeneration. Nitrogenous or other toxic retention is certainly not more than a contributory factor in the production of retinitis. Cholesterolemia is not a necessary factor. The origin of the edema of the nerve heads has not yet been determined. It may be toxic or ischemic or due to increased intracranial pressure from edema of the brain. Narrowing of the retinal arteries without other changes is seen chiefly in pregnant women and in acute glomerulonephritis. It is seen more frequently in association with other more severe changes. Sclerosis of the retinal arteries is found almost constantly in persons who have suffered from hypertension for a few years. It may occur in patients with general arteriosclerosis but without hypertension. Retinal arteriosclerosis in association with hemorrhages and sharply defined white patches, so-called arteriosclerotic retinopathy, is frequently seen in patients with hypertension but with normal renal function. Papilledema with "cotton wool" and hard patches and hemorrhages with or

without sclerosis of the arteries make up the typical nephritic neuroretinitis which is seen chiefly in malignant sclerosis and in the final decompensated stages of chronic glomerulonephritis but at times when renal function is normal. Narrowing of the retinal arteries means spasm and indicates only that the blood pressure is elevated. Sclerosis of the retinal arteries usually means that hypertension has existed for some time and that arteries elsewhere are similarly affected. It is not evidence of renal disease. It may indicate a tendency to apoplexy. Hemorrhages and sharply defined white patches in the retina do not indicate any special liability to death from renal disease, but they do suggest the possibility of cardiac or cerebral complications. They do not place a definite limit on life. The retinitis characterized by "cotton wool" patches and papilledema has been variously designated as nephritic retinitis, malignant hypertension neuroretinitis and retinitis of malignant hypertension. It indicates, in general, death within 2 years—usually from uremia but at times from apoplexy, cardiac failure or intercurrent disease. Occasionally, however, such a retinitis may clear up and renal failure may not develop. Papilledema occurring alone may be the first indication of nephritic retinitis or it may indicate increased intracranial pressure from edema or tumor of the brain, and observation is necessary for its final interpretation.

## OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF
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**The After-effect of Epinephrin Chlorid and Ephedrin Hydrochloride on the Mucosa of the Nasal Septum.**—The site of action, as well as the *modus operandi* of epinephrin and ephedrin when used topically, is a greatly debated question. Purposing to determine, if possible, the mode and site of action of these two drugs when applied locally to the nasal mucosa. Fox (*Arch. Otolaryngol.*, 1931, **13**, 255) reports results of histologic studies on septal tissues removed from 106 healthy adult rabbits. Under varying experimented conditions the nasal septums were removed and the mucosa prepared for microscopic examination according to techniques described in the text. It was concluded that a 1 to 1000 solution of epinephrin chlorid caused the mucosal vessels, at first constricted, to dilate after four hours and allow blood to escape into the perivascular bed and a chemotaxis-like behavior of the leukocytes; whereas, in the case of ephedrin hydrochlorid (2 per cent) the vessels remained unchanged after the 4-hour period. The author summarized by saying: "It seems rather, that epinephrin exerts some direct injury to the vessel walls."

**The Pharmacodynamics of Local Mucous Membrane Medication.**—The therapeutic objective of most localized medication is the production of astringency, antipathogenesis ranging from unfitting the

mucosa for bacterial growth and absorption of pathogenic products to complete destruction of microörganisms or mechanical protection, or a combination of these effects. Any therapeutic endeavor not considerate of the physiology and pathology of the tissues and the pharmacodynamic action of the drug employed, as based on those factors is empirical at best. Enumerating as important pharmacodynamic points such matters as insulation, viscosity, solubility, hydrogen-ion concentrate and the multiple effect of most drugs, SCHEFFEL (*Laryngoscope*, 1931, **41**, 274) discusses these factors as they relate to rational local mucosal medication. Attention is directed to the fact that: (1) Aqueous solutions or vehicles are practically free from the insulating drawbacks that appertain to some oily solutions; (2) that vehicular viscosity should depend largely upon the rate of absorbability desired; (3) that maximal therapeutic effects are dependent not only on the relative solubility of drug in its menstruum but also on a solubility; (4) that a hydrogen-ion concentration should closely approximate that of the tissues to be treated. The writer admonishes careful consideration of these basic principles before accepting or rejecting many preparations as having a scientific basis for rational topical therapy of mucous membranes.

## RADIOLOGY

UNDER THE CHARGE OF

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**Irradiation Therapy in Functional Ovarian Disorders.**—FORD (*Radiology*, 1931, **16**, 936) relates the results in 47 cases in which radiotherapy was administered primarily for habitual amenorrhea or for oligomenorrhea or sterility associated with these conditions, and in 29 cases in which this treatment was given primarily for dysmenorrhea. In the first group, by exposure of the ovaries or hypophysis to approximately 5 to 10 per cent of an erythema dose of Roentgen rays, reëstablishment of menses was obtained in 26 of the 47 cases. Menstruation has continued regularly in the majority of these patients for periods varying from a few months to two years. Seven pregnancies have occurred among 6 of the 24 married patients in this group, all of whom had previously been sterile. Two pregnancies were continuing at the time of this study, 2 have terminated in miscarriage, and 3 full-term children have been born, two of whom are living and well. Among the 29 patients with dysmenorrhea, relief of pain followed irradiation in 18. Although the duration of relief is extremely variable, by repeated irradiation a satisfactory result has been maintained as long as $3\frac{1}{2}$ years in 1 case. No evidence was found that repetition of treatment at intervals of 3 months or longer has adversely affected ovarian function.

**Radiography with Enlargement** (Microradiography).—It is known that if an object is moved away from the film and toward the source of radiation an enlarged roentgenographic image is obtained, but it is blurred, because the focal spot is not strictly a point but an area of appreciable size and a penumbra necessarily results. This disadvantage has been overcome by VALLEBONA (*Radiol.*, 1931, **17**, 340). He places a very small window between the object to be radiographed and the target of the tube; as a result the rays from the target follow a rectilinear path and produce an unblurred, enlarged image. The accessory apparatus is simple and consists of a series of lead disks with holes in them varying in size from 1 or 2 mm. to one half of a decimillimeter. The greater the distance of the object from the film, the smaller is the aperture required. According to the distance, the appropriate disk is selected and attached to the window of the tube cover. A magnified, sharp image is obtained. The method is especially applicable to the study of bone structure, and the author has used it successfully in cranial roentgenography.

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**The Roentgenologic Significance of Pyloric and Prepyloric Deformities.**—According to CAMP (*Radiology*, 1931, **16**, 847) it is a peculiar but significant fact that the pyloric segment of the stomach which is most accessible to roentgenologic examination, offers more diagnostic difficulties than any other. Sixty per cent of all gastric cancers, 69 per cent of benign gastric tumors and approximately 10 per cent of gastric ulcers are found in this area. This region is also a favorite site for spasm which is the arch deceiver of the roentgenologist. Fluoroscopic examination is indispensable for study of the pyloric segment, and is best accomplished by having the patient at first take only one or two swallows of the barium mixture which should be manipulated by the examiner so as to depict the internal topography of the stomach. Later the stomach can be completely filled with barium to study the gastric tonus, peristalsis and motility. In the consideration of ulcerating lesions in the pyloric region, it is noteworthy that here carcinoma outnumbers benign ulcer. Prepyloric ulcers also have a greater tendency to become malignant than ulcers elsewhere. Thus when ulceration is demonstrable the odds are in favor of a malignant lesion. Because of accessibility to examination pyloric cancer should be diagnosed earlier than cancer in other parts of the stomach. This is perhaps the case, yet the disease is not being diagnosed early enough. Of 2078 cases of gastric cancer seen at The Mayo Clinic between the years 1920 and 1924, 50 per cent were excluded from exploration as hopelessly inoperable, 25 per cent were explored but found to be inoperable, and resection was possible only in the remaining 25 per cent. Pyloric cancer may take the form of (1) a frank polypoid tumor with or without ulceration; (2) a scirrhous infiltrative growth; (3) a malignant ulcer, or (4) a benign tumor which has undergone malignant changes. The first form can scarcely escape discovery. Scirrhous cancer may be imitated by syphilis, prepyloric ulcer, pylorospasm and hypertrophic pyloric stenosis. The differential diagnosis of cancer rests on the persistence of the deformity, the slightly serrated outline, loss of flexibility, absence of peristalsis, obliteration of mucosal markings and the presence of a mass coinciding with the defect. An ulcer with a niche less than 2.5 cm.

in diameter has only 1 chance in 10 of being malignant; if it is larger than this the chances are 3 to 2 that it is malignant, and if larger than 3.5 cm. it is certainly cancerous. A high percentage of benign tumors undergo malignant change, and they are always open to suspicion.

## NEUROLOGY AND PSYCHIATRY

UNDER THE CHARGE OF

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**Encephalitic, Idiopathic and Arteriosclerotic Parkinsonism.**—KESCHNER and SLOANE (*Arch. Neurol. and Psychiat.*, 1931, **25**, 1011) report a clinicopathologic study of 7 cases of Parkinsonism. These cases are presented in detail both clinically and pathologically. They remark that "whereas the clinical course of the syndrome depends to a great extend on the nature of the pathologic process, it is obvious that its symptomatology does not depend entirely on the structural changes found in the nervous system after death." The substantia nigra was involved in every case except one diagnosed clinically as arteriosclerosis in which it showed only evidences of vascular sclerosis. The lesions in the locus cæruleus paralelled, to some extent, those in the substantia nigra. The pallidum seemed to have been mostly affected in the idiopathic cases. As to the involvement of the other basal ganglia, it did not seem to make much difference whether the case was encephalitic, idiopathic, or arteriosclerotic, so far as the site of the pathologic process was concerned. The changes in the cells were typical of a chronic degenerative process. The cases seemed to show that the generally accepted view that the neostriatum and pallidum are the predominating sites for the lesions in idiopathic Parkinsonism and the substantia nigra in encephalitic Parkinsonism must not be adhered to too slavishly in attempting to differentiate pathologically between these two types of disease. The diffuseness of the chronic inflammatory lesions in encephalitic Parkinsonism, the extensive secondary changes in the brain following disease of the vessels in the arteriosclerotic and the widespread degenerative lesions in the idiopathic form make attempts to correlate the clinical picture with the anatomic observations an unusually difficult task. The authors conclude "there is too little definite information as to the effects of disturbances of function and their relation to structural changes in the neural mechanism as the basis of the symptomatology of the various diseases of the extrapyramidal system. This is especially true in Parkinsonism. Hence the futility of attempting a definite differentiation between the various types of Parkinsonism without taking into consideration the history, symptomatology, clinical course and pathologic observations. Practically all one may say is that in many cases the presence or absence

of certain signs or symptoms of Parkinsonism during life will not always justify the clinician in giving an opinion as to what may be found at postmortem examination."

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**Dreams and Their Relationship to Recent Impressions.**—MALAMUD and LINDER (*Arch. Neurol. and Psychiat.*, 1931, **25**, 1081) present the results of experimental investigations in 16 cases undertaken with the purpose of finding out whether the factors uniformly occurring in dreams can be demonstrated experimentally. These observations form the central feature of the psychoanalytic theory of dream psychology. The psychoanalytic theory regards the dream as representative of a more or less disguised fulfillment of a wish that is otherwise repressed and does not gain access to the consciousness of the person when awake. This wish, which at one time has been actually experienced, but not gratified, remains as a latent force in the subconscious level and reappears in the dream only when stimulated by a suitable recent occurrence. The procedure was thus: The subject is taken into a quiet room and engaged in conversation for 5 minutes. The subject is allowed to look at a given picture for 30 seconds. He is conversed with for 5 more minutes. Then he is asked to describe the picture until his descriptive powers are exhausted. He is told that if he should have any dreams during the night he should remember them and give them to the examiner the next day. The patients were all mental cases in hospitals having varied diagnoses. The results of these experiments were as follows: (1) The factors regarded by the psychoanalytic theory as uniformly occurring in dreams were demonstrated in the dreams of a number of patients. (2) It is possible to produce them experimentally. (3) Some contents in the recent experiences of our subjects that were left out in their descriptions were subsequently shown to recur in their dreams. (4) These contents seemed to have a definite relationship to experiences in the earlier life of the person. (5) These latter two experiences "were found to be definitely related to those problems in the subjects' lives that, as far as could be judged, formed the central feature of the disease process."

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**The Incidence and Significance of Fingernail Biting in Children.**—WECHSLER (*Psychoanalytic Review*, 1931, **18**, 201) presents a study of 3000 children of both sexes, ranging from 1 to 17 years of age. He finds that fingernail biting under the age of 3 does not occur. The tendency first begins to manifest itself during the fourth year, rises slightly in the next, and then suddenly jumps up at the age of 6, from which year it maintains a fairly constant level until puberty. At the age of 12 for girls and the age of 14 for boys the percentage once more rises and continues at a high peak for 2 years. It then quickly recedes to a very low level at which it continues for the entire adult period. It becomes apparent that there is some connection between the incidence of fingernail biting and various periods of psychosexual development. The author discusses this relationship attempting a correlation between the two stating that nail biting is not a habit but a symptom of the œdipus situation and all treatment is "doomed to fail" unless the cause is attacked.

**Report of Results from Use of Ketogenic Diet and Ketogenic Diet With Water Restriction in a Series of Epileptics.**—Doolittle (*The Psychiatric Quarterly*, 1931, **5**, 2, 225) presents the results of his study of 25 epileptics with water restriction and modified ketogenic diet. These patients for a period of 4 weeks were segregated and given a regular diet and allowed to drink all the water they desired, day and night. The quantity of water consumed was recorded. All sedation was taken away from these cases with the exception of 2, with whom this was impossible. After a preliminary fasting of 12 hours, all these patients were placed on from 25 cc. to 44 cc. of 40 per cent cream every 4 hours with no water intake. This lasted for 40 hours. Following this all patients were put on a diet having acid ash, moderately ketogenic about as follows: Fat 140 to 180 gm., proteid 50 gm., carbohydrates 50 gm. At the same time these patients were placed on water restriction varying with the individual from 300 cc. to 630 cc. in 24 hours. The results observed by the writer may be tabulated as follows: (*a*) In the period of observation prior to water restriction, there were 67 petit mal and 116 grand mal seizures in the group per week. While on water restriction there were 80 petit mal and 75 grand mal seizures per week. Following the treatment the petit mal seizures dropped to 25 and the grand mal seizures rose to 87 per week. (*b*) Two cases showed very marked mental improvement. (*c*) The seizures did not decrease in the cases under dehydration with an increase in body temperature. Dehydration with hyperthermia was a serious combination. (*d*) Under ketogenic diet the cases showing the greatest tendency toward improvement were those of the idiopathic type. (*e*) Out of the 25 cases in which the modified ketogenic diet and water restriction therapy was tried, the author found one with whom he believed it could be called a success. Six patients showed quite marked improvement with respect to the grand mal seizures. Two showed slight improvement. The rest showed no improvement or apparently had an increase of seizures under treatment.

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**Encephalitis Periaxialis Diffusa: Schilder-Foix Disease.**—Coenen and Mir (*L'Encephale*, 1931, **26**, 357) describe a case of Schilder's disease in a man aged 41 years, which began with loss of sight in the left eye, headache, stiffness of the right arm, and a burning sensation round the abdomen; deafness of the left ear came on soon after, and within 3 weeks his right leg and left arm became weak and sensation was completely lost on the left half of the body. Both optic disks were swollen and pale. The patient died 43 days after the onset of the disease. At postmortem diffuse sclerosis and demyelination of the white matter of the cerebral hemispheres was found, with more discrete patches in the pons and cerebellum. The cortex was everywhere spared. In the histologic examination the most noteworthy finding was the large number of "mucocytes" in the areas of more recent demyelination. The authors confirm the findings of Grynfeltt and Pelissier and of Bailey and Schaltenbrand that mycocytes rise from acute swelling of the oligodendroglia by inhibition of the early products of myelin disintegration (protagonoid substances). They consider that in Schilder's encephalitis the disease process attacks first the oligodendroglia and that the degeneration of myelin is secondary to this.

## PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF
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**Hypertension in Relation to the Bloodvessels of the Medulla Oblongata.**—Several workers had previously attempted to show that hypertension was due to arteriosclerosis of the bloodvessels of the medulla oblongata. In the present study TUTHILL (*Arch. Path.*, 1931, **11**, 760) examined the bloodvessels of the medulla oblongata in the region of the obex in 24 cases of hypertension of varying duration, and in 35 cases in which the blood pressure was normal. In the cases with hypertension there were only 12 which showed an arteriosclerosis of the vessels of the medulla oblongata. The arterioles in the region of the olives and larger vessels in the center of the medulla were chiefly affected. Of the only 12 cases of hypertension slight or no arteriosclerosis of the vessels was found. Among the 35 cases in which the blood pressure was normal 6 showed arteriosclerosis of the vessels of the medulla oblongata. In none of the cases examined was arteriosclerosis confined solely to the vessels of the medulla oblongata. The author thus concluded that no proof was found that hypertension was the result of arteriosclerosis of the vessels of the medulla oblongata.

**Studies on Microglial Cells.**—According to the results of a preliminary series of experiments on cerebral embolism, through injections into the common carotids of 0.2 to 0.4 cc. of olive oil, undertaken by DADDI (*Le sperimentale*, 1931, **85**, 5) with a view to studying the different elements of the nerve tissue in relation to the metabolism of fat, the author believes that he can establish as extremely probable, if not certain, the presence in the microglial cells of a fat-absorbing property which is completely analogous to that characteristic for the cells of the reticulum. The astrocyte seems also to possess the quality of taking up the fat actively, and further experiments will be made to establish this claim.

**Oxychromatic Degeneration ("Intranuclear Inclusions") in Yellow Fever.**—In this lengthy communication TORRES (*Mem. d. instituto Oswaldo Cruz*, 1931, **25**, 148) reports his examination of tissues from 122 monkeys infected with yellow fever and 17 human cases which died in the Rio epidemic of 1928. The inclusion phenomenon is regarded by the author as a specific degenerative process. He disputes the assertion of Cowdry and Kitchen that intranuclear inclusions are formed "of colony-like masses of individual particles about the size of rickettsiæ," and says typical inclusions consist of a groundwork of acidophilic nucleoproteins and a stroma of linin, both of which are normal constituents of the nucleus. The author describes various

types of inclusions found by him in his large collection of material; he attempts to trace a progression from early to end-stage forms. A marked difference between the inclusions of man and monkeys is recorded. Only 3 of his 17 human cases presented inclusions, whereas the incidence was almost 100 per cent in monkeys. Of the 3 positive human cases 2 died within 48 hours of the onset of the disease, from which the author infers that the presence of inclusions is synchronous with the presence of the virus in the blood of the patient. He says the virus of the Rio epidemic was a "weak inclusion former" in man but "strong" in monkeys. The author refers to the inclusion phenomenon as a necrosis which attacks only determined constituents of the nucleus, leaving the rest unaltered. He suggests the term "meronecrosis" (from *meros*, a part) as descriptive of the inclusion phenomenon in all the virus diseases.

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**The Effect of Prolonged Exposure of the Siliceous Spicules of a Freshwater Sponge (Spongilla Fragilis) to the Action of Animal Tissues: A Contribution to the Pathogenesis of Silicosis in Man.**—The spicules which MILLS (*Am. J. Hyg.*, 1931, **13**, 224) recovered from fresh water sponges contained 18.3 per cent silicon dioxid. These the author injected intramuscularly into various animals, 7 in all. After varying periods ranging between 182 and 472 days the lesions were examined and the spicules recovered. The lesions were negligible, but the spicules were reduced in size indicating that they had undergone partial solution. In the case of 1 animal the spicules were injected into lung, where they remained 482 days. When the animal was killed a moderate degree of patchy fibrosis was found at the site of the injection. From these results the author states "This confirms the assumption held by many students of silicosis that particles of siliceous material are gradually converted into the colloidal state and as such exert a fibroplastic influence on the lungs of miners and other exposed industrial workers." The author does not give the size of the silica spicules he used, but from the photographs they seem to be about 0.3 mm. in length on the average. This is a dimension many times in excess of the common silica dust particle found in miner's lungs. The experiments lack controls and on the whole fail to convince one that the author has produced an experimental analogy of human silicosis.

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**The Rate and Site of Removal of Bacteria from the Blood in Blood Stream Infections.**—OTTENBERG (*Arch. Path.*, 1931, **11**, 766) showed, from the results of simultaneous blood cultures from both jugular veins and from an arm vein in cases of lateral sinus thrombosis, that there were always fewer bacteria in the arm vein than in the jugulars. In a series of control cases (bacterial endocarditis and sepsis) the colonies per cubic centimeter of blood were for practical purposes the same in all veins. The differences cannot be explained by dilution with the general circulation. The bacteria are evidently killed or are very rapidly filtered from the circulation. The actual site of filtration of the bacteria could not be proved, but the evidence that in a bacteremia the number of bacteria from an artery and that from a vein of an extremity are practically the same was offered to show that they were not removed by the peripheral tissues of the extremities. Other sites as lung and liver where

filtration probably largely occurs, are discussed. Reasons were given for believing that in many cases of sinus thrombosis bacteria were fed into the blood stream somewhat steadily over a period of time rather than in momentary "showers."

## HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

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**Typhus Fever.**—A Virus of the Typhus Type Derived from Fleas Collected from Wild Rats.—DYER, RUMREICH and BADGER (*Public Health Reports*, 1931, **46**, 334) note that various investigators have suggested a vector for typhus in addition to the body louse which is held responsible for the disease in most parts of the world. In connection with their epidemiologic investigations in the city of Baltimore it was noted that there was a heavy infestation with rats in localities in which certain cases of typhus occurred. Fleas taken from these environments emulsified and injected into guinea pigs gave rise, after a suitable incubation period, to a febrile reaction not to be differentiated from that induced by typhus fever in the guinea pig. Monkeys had similar reactions and the blood of these animals developed agglutinins for the proteus organism that has proven so useful in the diagnosis of typhus in man. Rabbits gave similar results. Finally cross-immunity tests were made which indicated that the virus derived from fleas was not to be differentiated from that derived from human cases of endemic typhus of the new-world variety.

**Transmission to the Third Generation of Antitoxin Derived by Active Immunization of the First Generation.**—SUGG, RICHARDSON and NEILL (*J. Immunol.*, 1931, **20**, 255) report an example of a guinea pig of the second generation transmitting to its own offspring (third generation) small amounts of antitoxin originally derived by active immunization of the first generation. Previous reports of failure of transmission were probably due to quantitative inadequacy of the immunity originally transmitted to the females of the second generation to persist to the time of birth of the third generation.

**Excessive Ultraviolet Irradiation.**—HESS and SMITH (*Am. J. Dis. Child.*, 1931, **41** 775) state that in spite of the fact that ultraviolet irradiation has been made use of during the past 10 years or more to an increasing extent, no prolonged observations have been made on the effect of this remarkable remedial agent on the growth and functions

of the body. This is all the more remarkable, as from time to time the question has been raised as to whether these radiations may not inflict harm as well as be of advantage to the animal body. With this in mind, two series of rats were irradiated with the mercury-vapor lamp for a period of from 5 to 6 months or were given viosterol. Male as well as female animals were used; those in the first series were litter-mates, those in the second series, although not litter mates, were the progeny of the first. Three intensities of irradiation were given, mild, moderate and severe. The viosterol was given in small as well as in excessive amounts. The main object of the experiment was to note whether prolonged and intense irradiation or large doses of viosterol had a deleterious effect on the animals, as evinced by the rate of growth and by the size and appearance of the endocrine glands. The growth of the animals subjected to marked intensities of ultraviolet irradiation or given large amounts of viosterol was as good as that of animals which had lived under similar conditions but had not been subjected to irradiation or given viosterol. No difference was noted at necropsy between the endocrine glands of the treated and those of the untreated animals.

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**Significance of Positive Wassermann and Kahn Reactions in Leprosy.**—BADGER (*U. S. Pub. Health Rep.*, 1931, **46**, 957) reviews the literature of the subject and presents the results of his own studies and summarizes his experience as follows: (1) There occurred an abnormally high incidence of positive serum reactions in the cases studied. (2) The positive reactions occurred nearly twice as frequently among the females as the males. (3) The positive reactions were more frequent among the patients under than those over 20 years of age. (4) Positive reactions were three times as frequent among the lepers as among a control group. (5) Definite changes in the serum reactions correlated with changes in the clinical manifestations of the leprosy were observed.

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**Rocky Mountain Spotted Fever (Eastern Type).**—Transmission by the American Dog Tic (Dermacentor variabilis). DYER, BADGER and RUMREICH (*U. S. Pub. Health Rep.*, 1931, **46**, 1403) recall that in a recent paper they had shown there prevails in the eastern part of the United States an infection of the Rocky Mountain spotted fever type with certain differences from the eastern type so far as lesions in animals are concerned, but immunologically identical. In the present paper they record the successful transmission of the eastern type of spotted fever by means of the common dog tick (Dermacentor variabilis). Details of the transmission and immunity tests are given together with the histopathology.

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**Prevalence of Undulant Fever in the United States.**—HASSELTINE (*U. S. Pub. Health Rep.*, 1931, **46**, 1519) has studied the prevalence of undulant fever for 1929 and 1930. A total of 952 cases was reported for 1929 and 1387 for 1930, and it is indicated that these figures are too low to portray the actual prevalence of the infection. The disease seems to show the lowest incidence in the first quarter of the year with the highest in the third quarter.

# PHYSIOLOGY

PROCEEDINGS OF

## THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF NOVEMBER 9, 1931

**The Results of Direct Intrafollicular Injection of Extracts of Urine of Pregnancy.**—MAURICE H. FRIEDMAN (from the Laboratory of Physiology, University of Pennsylvania). Although the biologic effects of urine of pregnancy are similar to those obtained with extracts of the anterior lobe of the pituitary, there has been no conclusive demonstration that the effective substances found in pregnant urine are derived from the pituitary. There are, indeed, many who believe that the action of urine of pregnancy is an indirect one, involving the stimulation of the pituitary in the injected animal. To determine whether or not extracts of urine of pregnancy were capable of exerting a direct effect on the ovary, a series of experiments were performed in which the follicles in one ovary of an estral rabbit were injected with minute quantities of an extract of urine of pregnancy. The other ovary in the animal was untouched. In 20 of 30 animals this procedure led to the formation of corpora lutea in the injected ovary, while the contralateral ovary showed no change whatsoever, presenting only large, unaltered follicles. In 6 control experiments physiologic saline was injected into the ovarian follicles instead of the urine extract, and in these instances no lutein tissue was developed. It is apparent, therefore, that extracts of urine of pregnancy when injected directly into an ovarian follicle may produce luteinization of the injected follicle in the absence of any general humoral change of sufficient magnitude to produce a change in uninjected follicles.

**Anion Cation Studies in Liver and Gall-bladder Bile.**—I. S. RAVDIN, C. S. JOHNSTON, C. RIEGEL and J. H. AUSTIN (from the Laboratories of Surgical Research and Research Medicine, University of Pennsylvania). In studies of the individual constituents of the bile subjected to gall-bladder activity in a bile-free gall bladder the total osmolar concentration tended to approach that of serum when sodium chloride was used. Solutions of calcium lactate were concentrated during day periods in the normal gall bladder although calcium was absorbed. Bile salts, either the glycocholate or taurocholate, were concentrated, although these studies could be conducted for only short periods because the bile salts caused a violent inflammation of the gall-bladder wall, which resulted in hemorrhage. Cholesterol in suspension was concentrated, and we found little if any evidence that it was absorbed. A mixture of the bile salts and a suspension of cholesterol was then studied. Bile salts were very slowly absorbed; cholesterol was not absorbed. The cholesterol did not precipitate out of the suspension as water was absorbed, as it did when a simple suspension was used, and the gall-bladder wall was not injured as early as it had been when bile salt alone was used.

We have studied the anion cation content of hepatic bile and the changes in the anion cation content when hepatic bile was subjected to gall-bladder activity.

The hepatic bile in known amounts was introduced into the bile-free gall bladder and permitted to remain there for from 2 to 24 hours. It was removed with a Luer syringe. Each animal was tested at the time of operation in order to be sure that we could recover the amount of fluid introduced. After catheterization and washing of the gall bladder normal saline solution was left in to test the absorptive function of the viscus and to ascertain whether accessory ducts had been overlooked. As long as the gall bladder remained normal fluid was absorbed. The exact amount varied considerably. Estimations of the pigment concentrations in hepatic bile subjected to gall-bladder activity have shown increases in concentration of this substance over a 24-hour period, varying from 5 to 17 times that of the bile introduced. The minimum figure is in agreement with the low figures published by Rous and McMaster, but the maximum figures are considerably higher than their figures.

Hepatic bile is more variable in its electrolyte composition than is serum. This is true for different animals and for the same animal at different times. It is higher in base, total anion and, as a rule, in bicarbonate, while chloride tends to be somewhat lower than that of serum. The bile salt concentration has varied from 15.6 to 66 mille equivalents per liter. The calcium content of hepatic bile is nearly always higher than that of serum and is much more variable. The pH has varied from 7.1 to 8.6. A comparison of the estimated anion cation content of hepatic bile shows that unknown anions account for a median of about 12 mille equivalents per liter.

The amount of anion which might be accounted for by the small protein content of hepatic bile is not more than a few mille equivalents per liter. The amount bound by phosphoric acid either inorganic or in lipoid combination, by fatty acids or by bile pigments, is unknown.

After subjecting a single injection of hepatic bile to gall-bladder activity for a short period, one finds considerable variability in the composition of the bile. In 7 of the 9 instances where complete studies were made the per cent decrease of the total estimated anion was greater than that of the cation. In the remaining 2 experiments anion and cation showed the same per cent decrease.

An analysis of our data shows that bile salt and undetermined anion increase in concentration. In the 2 experiments where bile salt concentration increased above 40 per cent the total base concentration increased. If the gall bladder is constantly receiving bile and the bile salt and undetermined anion concentrations are increasing the retained base will also increase in concentration. We have obtained a bile salt concentration as high as 194 mille equivalents per liter from a single injection of hepatic bile. The exact time at which base concentration will increase will depend upon the rapidity with which the bile salt undetermined anion concentration increases.

The composition of the bile after stay in the gall bladder is the resultant of an absorption of water, accompanied by some bile salts and a disproportionately high absorption of chloride and bicarbonate. The exact change in the known anions perhaps bears some relation to the increase in concentration of the bile salts and unknown anions.

The change in pH is probably dependent on an increase in concentration of some unknown acid. The variability in the composition of the bile removed from the gall bladder is to be attributed to the fact that we are dealing with a resultant of different rates of absorption of the various components rather than with a condition of equilibrium. When bile is constantly added to the amount in the gall bladder, base undoubtedly rises.

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**On Osmotic Properties of Living Cell Fragments.**—Balduin Lucké (from the Laboratory of Pathology, University of Pennsylvania). It is well known that the normal living cell acts as if it possessed a semipermeable membrane; that is to say, a protoplasmic layer which, while permeable to water, is more or less impermeable to many dissolved substances. Upon this conception are based the majority of the theories of selective permeability and of osmotic behavior of cells.

Little is known about the properties of reconstructed membranes, *i. e.*, membranes that have in some sense been reformed. It is known that when a cell is mechanically injured, by tearing, cutting or crushing, a new surface film will form almost instantaneously (at least under favorable conditions) over the injured surface or over the protoplasm which has been extruded. Such newly formed films have the same selective permeability with respect to various dyes as has the whole cell.

The technique lately developed by E. N. Harvey of dividing spherical cells (unfertilized eggs of the sea urchin) into two nearly equal spheres by means of centrifugation in a medium of proper density, affords an opportunity of studying the properties of reconstructed surface membranes of cell fragments that have suffered no injury, for upon insemination these fragments form fertilization membranes and subsequently undergo cleavage. Since division of a sphere considerably increases surface area, the surface of the newly formed fragments must in some sense be a reconstructed one. The question we wish to answer is, do such reconstructed membranes have the same properties of semipermeability as the whole cell?

One of the best methods for studying semipermeability of cells is the osmotic method. With suitable cells, in this case the living unfertilized eggs of the sea urchin, it has been shown that their volume changes in anisotonic solutions are adequately accounted for by the law of Boyle-van't Hoff, which relates the volume of a closed osmotic system to the osmotic pressure of the surrounding medium with which it is in equilibrium. Stated alternatively, we have previously found that with this material the product of volume and pressure is approximately constant, if correction is made for volume occupied by osmotically inactive material. From these results the inference may be drawn that the semipermeability of the cell surface is nearly perfect. If the law of Boyle-van't Hoff should also hold for cell fragments it would indicate that their surfaces were similar to those of the original cells. That this law does hold was shown by measuring the volume of the cell fragments in three different concentrations of sea water with which they had been brought in osmotic equilibrium. Further proof of the semipermeability of the surface was obtained by measuring previously swollen cells after they had again attained equilibrium in ordinary sea water. It was found that the fragments returned to within 2 per cent of their

original size. From these experiments it is concluded that the reconstructed surface of living cell fragments is similar to that of the original cell; that it is an approximately semipermeable one.

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**Arteriovenous Anastomoses.**—E. R. Clark, E. L. Clark and E. A. Swenson (from the Department of Anatomy, University of Pennsylvania). Direct connections between arteries and veins, by passages decidedly larger than capillaries, which have been called arteriovenous anastomoses, have been described by Sucquet (1862), Hyett (1864), Hoyer (1877), Pourceret (1885), Grosser (1902) and Grant (1930). There is general agreement that they exist normally in the erectile tissue of the sex organs, in the balls and nail beds of fingers and toes, in the tip of the nose, the tip of the tail and in the outer ears of various mammals. While they have been described in other locations, their existence elsewhere has not been established. The best descriptions of them, made upon injected and fixed material, are those of Hoyer and Grosser. According to them, arteriovenous anastomoses are quite definite structures, ranging in inside diameter from 10 to 50 micra (except for one in the tip of the bat's wing, which may reach a diameter of 150 micra) with a wall which greatly exceeds in thickness that of the arteriole which precedes it. The smooth muscle has, in addition to the usual circular arrangement, an inner longitudinal layer and an outer layer of oblique cells.

Grant (1930), whose studies have paralleled our own, has made interesting observations on arteriovenous anastomoses in the rabbit's ear as seen through the intact skin, and has described their behavior under a variety of experimental conditions. He considers that they play an important rôle in temperature regulation in the rabbit's ear and the tip of the human finger.

Our attention was called to them first in the fall of 1929, when we saw them in the type of transparent chambers introduced in the rabbit's ear in which the preformed tissue is retained, with its original vessels and nerves. They were made accessible to microscopic study by the removal of the cartilage and the skin of the inner side of the ear, and the substitution of a thin sheet of mica. These structures were demonstrated in the living animal at the meeting of the American Association of Anatomists at the University of Virginia, in April, 1930, and at the International Congress of Anatomists in Amsterdam, in August of that year.

Studies of these interesting structures have only begun, but already many suggestive observations have been made, while the possibilities for the study not only of their function but also of the factors responsible for their formation seem to be unlimited, with the methods for bringing them under observation in the transparent double-walled chambers. It was found that arteriovenous anastomoses are normally present in the rabbit's ear to the extent of from 40 to 50 in an area approximately 1 cm. in diameter, and the special preparation enabled the observer to make precise observations upon their normal behavior as well as their behavior under experimental conditions for many hours a day, and for weeks and months. It was found that they are definite and, certainly in most cases, permanent structures. Some of them are straight and some are twisted or coiled. They may occur singly or in groups of 2 to 8. They possess a thick wall which suddenly thins to

a single endothelial, noncontractile layer at the venous end which always remains wide, giving a funnel-shaped appearance.

In behavior it has been noted that they are extraordinarily contractile, the most contractile of all the parts of the peripheral vascular system in the ear. The arteries and arterioles of the ear undergo frequent spontaneous active contractions, usually showing a periodicity of two or three contractions per minute. These general contractions usually involve also the arteriovenous anastomoses. But between such contractions there may be separate contractions of some arteriovenous anastomoses, and it is not uncommon to see an individual arteriovenous anastomosis remain contracted for hours or even days, while a neighboring one may be showing four to eight alternate contractions and dilatations per minute. The arteriovenous anastomoses contract simultaneously with all the peripheral arteries and arterioles following stimulation of the whole animal.

In addition to the study of arteriovenous anastomoses in the preformed tissue, it has been possible to observe the new formation of definite and permanent ones in new tissue which has grown into an empty space left between the mica and a kodaloid table in a second type of transparent chamber, which we have called the "round table" chamber. In 1 such specimen installed in July, 1930, taken to Amsterdam for demontration and brought back to America, four arteriovenous anastomoses were observed in October, 1930. They were watched for several months and during that time showed no evidence of nerve-controlled contraction. In March, 1931, 8 months after installation, one of the four showed definite contractions which synchronized with the contractions of the main arteries of the ear. In June, 1931, at 11 months, two others showed similar synchronized contractions. At that time, and in July, the fourth one still failed to show synchronized contraction.

It was possible to obtain motion pictures of these four arteriovenous anastomoses, of one of them in March, 1931, and of all four in June, as well as motion pictures of similar structures in a second rabbit in a chamber installed and cared for by Dr. R. O. Rex in our laboratory. (A reel of motion pictures showing both contracting and noncontracting arteriovenous anastomoses was shown.)

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